=> fil reg
FILE 'REGISTRY' ENTERED AT 15:08:18 ON 18 MAR 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 17 MAR 2003 HIGHEST RN 499763-93-8
DICTIONARY FILE UPDATES: 17 MAR 2003 HIGHEST RN 499763-93-8

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

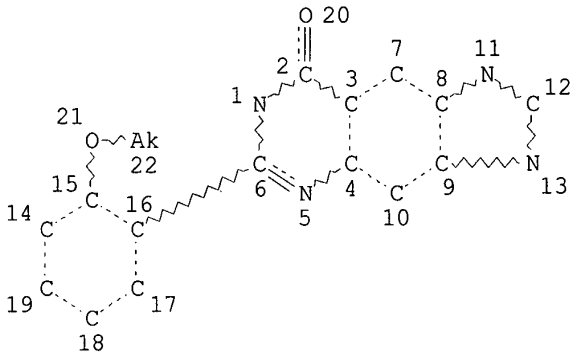
Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d stat que l25

L16 STR



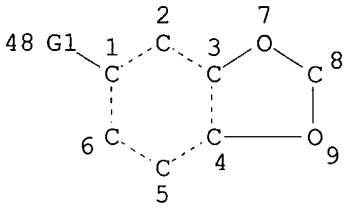
e) & f)

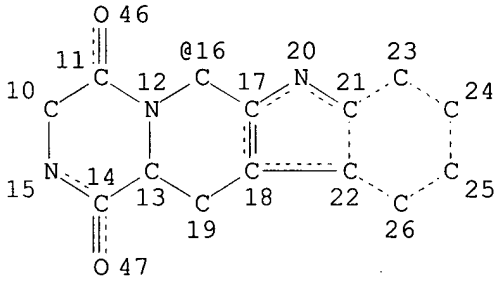
full file search done looking for any of the following 3 structures

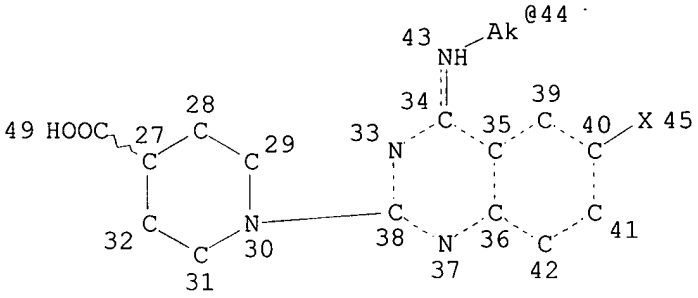
NODE ATTRIBUTES:
CONNECT IS E1 RC AT 22
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 22

STEREO ATTRIBUTES: NONE
L18 STR





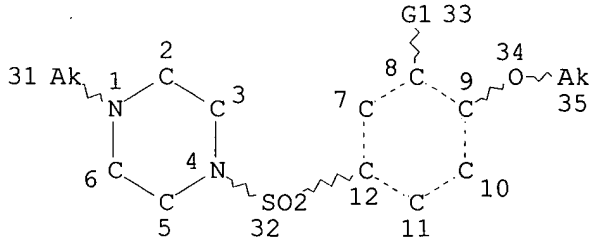


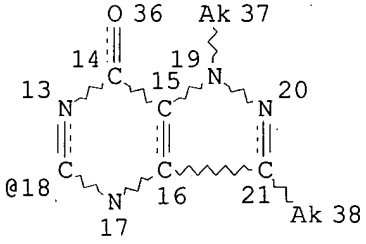
b) & d)

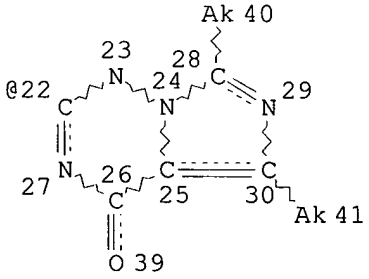
VAR G1=16/44
NODE ATTRIBUTES:
CONNECT IS E2 RC AT 44
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 49

STEREO ATTRIBUTES: NONE
L20 STR







a) & c)

VAR G1=18/22
NODE ATTRIBUTES:

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CONNECT IS E1  RC AT  31
CONNECT IS E1  RC AT  35
CONNECT IS E1  RC AT  37
CONNECT IS E1  RC AT  38
CONNECT IS E1  RC AT  40
CONNECT IS E1  RC AT  41
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  41

STEREO ATTRIBUTES: NONE
L25          368 SEA FILE=REGISTRY SSS FUL L16 OR L18 OR L20

100.0% PROCESSED   2563 ITERATIONS                    368 ANSWERS
SEARCH TIME: 00.00.01


=> fil capl; d que nos l27;d que nos l29

FILE 'CAPLUS' ENTERED AT 15:08:19 ON 18 MAR 2003
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FILE COVERS 1907 - 18 Mar 2003  VOL 138 ISS 12
FILE LAST UPDATED: 17 Mar 2003  (20030317/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


L14         2619 SEA FILE=CAPLUS ABB=ON  PULMONARY(L)HYPERTENS?/OBI
L16              STR
L18              STR
L20              STR
L25          368 SEA FILE=REGISTRY SSS FUL L16 OR L18 OR L20
L26          639 SEA FILE=CAPLUS ABB=ON  L25
L27           17 SEA FILE=CAPLUS ABB=ON  L14 AND L26


L16              STR
L18              STR
L20              STR
L25          368 SEA FILE=REGISTRY SSS FUL L16 OR L18 OR L20
L26          639 SEA FILE=CAPLUS ABB=ON  L25
L28        10809 SEA FILE=CAPLUS ABB=ON  VASCULAR?(2A)RESIST?
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L29 11 SEA FILE=CAPLUS ABB=ON L28 AND L26

=> s l27 or l29

L45 24 L27 OR L29

=> fil uspatf; d que nos l39

FILE 'USPATFULL' ENTERED AT 15:08:21 ON 18 MAR 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 18 Mar 2003 (20030318/PD)
FILE LAST UPDATED: 18 Mar 2003 (20030318/ED)
HIGHEST GRANTED PATENT NUMBER: US6536043
HIGHEST APPLICATION PUBLICATION NUMBER: US2003051284
CA INDEXING IS CURRENT THROUGH 18 Mar 2003 (20030318/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 18 Mar 2003 (20030318/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2002
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2002

>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
>>> USPATFULL. A USPATFULL record contains not only the original <<<
>>> published document but also a list of any subsequent <<<
>>> publications. The publication number, patent kind code, and <<<
>>> publication date for all the US publications for an invention <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<

>>> USPATFULL and USPAT2 can be accessed and searched together <<<
>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
>>> enter this cluster. <<<
>>> <<<
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication. <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.

L16 STR
L18 STR
L20 STR
L25 368 SEA FILE=REGISTRY SSS FUL L16 OR L18 OR L20
L36 170 SEA FILE=USPATFULL ABB=ON L25
L37 114 SEA FILE=USPATFULL ABB=ON (VASCULAR?(2A)RESIST?)/IT,TI,AB,CLM

L38 338 SEA FILE=USPATFULL ABB=ON (PULMONARY OR LUNG#)(2A)HYPERTENS?/I
T,TI,AB,CLM
L39 6 SEA FILE=USPATFULL ABB=ON L36 AND (L37 OR L38)

=> fil medl; d que nos 143

FILE 'MEDLINE' ENTERED AT 15:08:21 ON 18 MAR 2003

FILE LAST UPDATED: 16 MAR 2003 (20030316/UP). FILE COVERS 1958 TO DATE.

On June 9, 2002, MEDLINE was reloaded. See HELP RLOAD for details.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2003 vocabulary. See http://www.nlm.nih.gov/mesh/summ2003.html for a description on changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L16             STR
L18             STR
L20             STR
L25         368 SEA FILE=REGISTRY SSS FUL L16 OR L18 OR L20
L40        1087 SEA FILE=MEDLINE ABB=ON  L25
L41       30421 SEA FILE=MEDLINE ABB=ON  VASCULAR RESISTANCE+NT/CT
L42       12986 SEA FILE=MEDLINE ABB=ON  HYPERTENSION, PULMONARY+NT/CT
L43          43 SEA FILE=MEDLINE ABB=ON  L40 AND (L41 OR L42)
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=> dup rem l45,l39,l43
FILE 'CAPLUS' ENTERED AT 15:08:35 ON 18 MAR 2003
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FILE 'USPATFULL' ENTERED AT 15:08:35 ON 18 MAR 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'MEDLINE' ENTERED AT 15:08:35 ON 18 MAR 2003
PROCESSING COMPLETED FOR L45
PROCESSING COMPLETED FOR L39
PROCESSING COMPLETED FOR L43
L46          63 DUP REM L45 L39 L43 (10 DUPLICATES REMOVED)
                ANSWERS '1-24' FROM FILE CAPLUS
                ANSWERS '25-29' FROM FILE USPATFULL
                ANSWERS '30-63' FROM FILE MEDLINE

=> d ibib abs hitstr 1-29; d iall 30-63

L46  ANSWER 1 OF 63  CAPLUS  COPYRIGHT 2003 ACS        DUPLICATE 1
ACCESSION NUMBER:         2002:470570  CAPLUS
DOCUMENT NUMBER:          137:72960
TITLE:                    Oral sildenafil is an effective and specific
                          pulmonary vasodilator in patients with
                          pulmonary arterial hypertension.
                          comparison with inhaled nitric oxide
AUTHOR(S):                Michelakis, Evangelos; Tymchak, Wayne; Lien, Dale;
                          Webster, Linda; Hashimoto, Kyoko; Archer, Stephen
CORPORATE SOURCE:         Department of Medicine, University of Alberta,
                          Edmonton, AB, Can.
SOURCE:                   Circulation (2002), 105(20), 2398-2403
                          CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER:                Lippincott Williams & Wilkins
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   The prognosis of patients with severe pulmonary hypertension (PHT) is
     poor. The aim of this study was to det. prognosis and guide therapy, an
     acute hemodynamic trial of selective pulmonary vasodilators, usually
     inhaled nitric oxide (iNO), was performed. We hypothesized that oral
     sildenafil, a phosphodiesterase-5 inhibitor, is a safe and effective
     alternative to iNO. We studied 13 consecutive patients (mean.+-.SEM,
     44.+-.2 yr of age; 9 women) referred for consideration of heart-lung
```

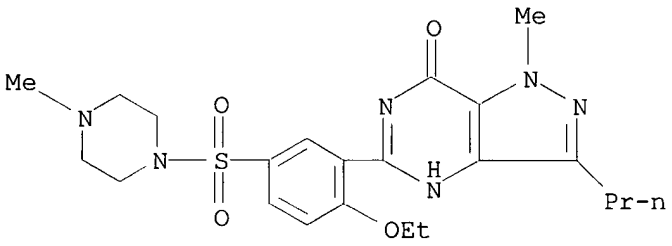

[redacted]

transplantation or as a guide to medical therapy. All but one were functional class III or IV. Patients had primary PHT (n=9), pulmonary arterial hypertension (n=2), or secondary PHT (n=2). Hemodynamics and serum cyclic guanosine-monophosphate levels (cGMP) were measured at baseline and at peak effects of iNO (80 ppm), sildenafil (75 mg), and their combination. The decrease in pulmonary **vascular resistance** was similar with iNO (-19.+-.5%) and sildenafil (-27.+-.3%), whereas sildenafil+iNO was more effective than iNO alone (-32.+-.5%, P<0.003). Sildenafil and sildenafil+iNO increased cardiac index (17.+-.5% and 17.+-.4%, resp.), whereas iNO did not (-0.2.+-.2.0%, P<0.003). INO increased, whereas sildenafil tended to decrease, pulmonary capillary wedge pressure (+15.+-.6 vs. -9.+-.7%, P<0.0007). Systemic arterial pressure was similar among groups and did not decrease with treatment. CGMP levels increased similarly with iNO and sildenafil, and their combination synergistically elevated cGMP (P<0.0001). A single oral dose of sildenafil is as effective and selective a pulmonary vasodilator as iNO. Sildenafil may be superior to iNO in that it increases cardiac output and does not increase wedge pressure. Future studies are indicated to establish whether sildenafil could be effective over a longer duration.

IT **139755-83-2**, Sildenafil
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral sildenafil for specific **pulmonary** vasodilator in patients with **pulmonary** arterial **hypertension** in comparison to inhaled nitric oxide)

RN 139755-83-2 CAPLUS

CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 2 OF 63 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 2

ACCESSION NUMBER: 2002:310575 CAPLUS
DOCUMENT NUMBER: 136:395660
TITLE: Combination therapy with oral sildenafil and inhaled iloprost for severe **pulmonary hypertension**
AUTHOR(S): Ghofrani, Hossein Ardeschir; Wiedemann, Ralph; Rose, Frank; Olschewski, Horst; Schermuly, Ralph Theo; Weissmann, Norbert; Seeger, Werner; Grimminger, Friedrich
CORPORATE SOURCE: University Hospital, Justus-Liebig-University, Giessen, Germany
SOURCE: Annals of Internal Medicine (2002), 136(7), 515-522
CODEN: AIMEAS; ISSN: 0003-4819
PUBLISHER: American College of Physicians-American Society of Internal Medicine
DOCUMENT TYPE: Journal
LANGUAGE: English

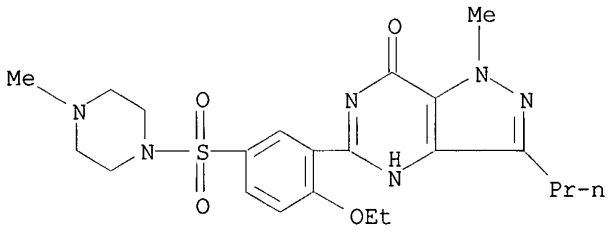
Searched by Barb O'Bryen, STIC 308-4291

AB Background: Inhalation of the stable prostacyclin analog iloprost is being studied for treatment of pulmonary hypertension. The selective phosphodiesterase-5 inhibitor sildenafil has been reported to cause pulmonary vasodilatation. Objective: To evaluate the safety and effectiveness of oral sildenafil, alone and in combination with inhaled iloprost, for treatment of pulmonary hypertension. Design: Randomized, controlled, open-label trial. Setting: Intensive care unit. Patients: 30 patients with severe pulmonary arterial hypertension (n = 16), chronic thromboembolic pulmonary hypertension (n = 13), or pulmonary hypertension due to aplasia of the left pulmonary artery (n = 1), all classified as New York Heart Assocn. class III or IV. Intervention: All patients received inhaled nitric oxide and aerosolized iloprost (inhaled dose, 2.8 .mu.g). They were then randomly assigned to receive 12.5 mg of oral sildenafil, 50 mg of sildenafil, 12.5 mg of sildenafil plus inhaled iloprost, or 50 mg of sildenafil plus inhaled iloprost. Measurements: Systemic and pulmonary arterial pressure, pulmonary arterial occlusion pressure, cardiac output, central venous pressure, peripheral arterial oxygen satn., and arterial and mixed venous blood gases were measured during right-heart catheterization by using a Swan-Ganz catheter. Results: In rank order of pulmonary vasodilatory potency (max. redn. of pulmonary **vascular resistance** and increase in cardiac index), 50 mg of sildenafil plus iloprost was most effective, followed by 12.5 mg of sildenafil plus iloprost. Iloprost alone and 50 mg of sildenafil were almost equally effective but were less potent than the combination regimens, and the least potent treatments were 12.5 mg of sildenafil and nitric oxide. In patients who received 50 mg of sildenafil plus iloprost, the max. change in pulmonary vasodilatory potency was -44.2% (95% Cl, -49.5% to -38.8%), compared with -14.1% (Cl, -19.1% to -9.2%) in response to nitric oxide. With administration of 50 mg of sildenafil plus iloprost, the area under the curve for redn. in pulmonary vasodilatory resistance surpassed that of administration of 50 mg of sildenafil alone and iloprost alone combined, the vasodilatory effect lasted longer than 3 h, and systemic arterial pressure and arterial oxygenation were maintained. No serious adverse events occurred. Conclusion: Although limited by the small sample and lack of long-term observations, the study shows that oral sildenafil is a potent pulmonary vasodilator that acts synergistically with inhaled iloprost to cause strong pulmonary vasodilatation in both severe pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.

IT **139755-83-2**, Sildenafil
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral sildenafil monotherapy vs. combination therapy with inhaled iloprost for **pulmonary hypertension** patients)

RN 139755-83-2 CAPLUS

CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

[redacted]

L46 ANSWER 3 OF 63 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 3
ACCESSION NUMBER: 2001:916407 CAPLUS
DOCUMENT NUMBER: 136:53755
TITLE: Synthesis of nitrosated and nitrosylated (hetero)cyclic phosphodiesterase inhibitors used in treatment of sexual dysfunction
INVENTOR(S): Garvey, David S.; Saenz de Tejada, Inigo; Earl, Richard A.; Khanapure, Subhash P.
PATENT ASSIGNEE(S): Nitromed, Inc., USA
SOURCE: U.S., 117 pp., Cont.-in-part of U.S. 5,958,926.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6331543	B1	20011218	US 1999-387727	19990901
US 5874437	A	19990223	US 1996-740764	19961101
WO 9819672	A1	19980514	WO 1997-US19870	19971031
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5958926	A	19990928	US 1998-145142	19980901
US 2002019405	A1	20020214	US 2001-941691	20010830
US 6462044	B2	20021008		
US 2003023087	A1	20030130	US 2002-216886	20020813

PRIORITY APPLN. INFO.:
US 1996-740764 A2 19961101
WO 1997-US19870 A2 19971031
US 1998-145142 A2 19980901
US 1999-387727 A1 19990901
US 2001-941691 A3 20010830

OTHER SOURCE(S): MARPAT 136:53755
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

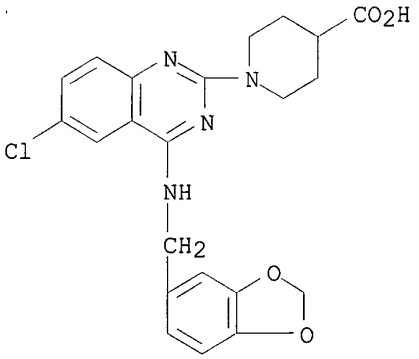
AB Compds. I-V, derivs. thereof, and certain substituted Ph and phthalzaine derivs. were claimed [D2 = H, alkyl, D; D = NO, NO2, alkyl, acyl, phosphoryl, silyl, etc.; A1-3 comprise the other subunits of a 5- or 6-membered monocyclic arom. ring; R8 = H, (halo)alkyl; p = 1-10; R24 = H, cyclohexyl, piperidinyl, etc., with the proviso that at least one of A1-3, J, or R24 contains T-Q or D; T = bond, O, S(O), amino; Q = NO, NO2; D1 = D or H; R37 = (hetero)aryl; R38 = H, halo, alkyl; G1 = alkyl, alkenyl or is part of a ring fused to the piperidine moiety of III; G4 = O, S; R40 = H, alkyl, haloalkyl, halo, etc.; R41 = alkyl, hydroxyalkyl, alkylcarboxy, etc.; R42 = aryl, alkylaryl, alkyloxyaryl; T1 = alkyl, oxyalkyl, thioalkyl, aminoalkyl]. Two synthetic examples were provided. E.g., the S-nitroso deriv. of the 3-mercapto-3-methylbutyric acid ester of dipyridamole (VI) was prepd. in 4 steps from dipyridamole in 3.5% overall yield. VI at doses of 10 and 30 .mu.M was more efficacious in relaxing phenylephrine-induced tissue contraction than was the known phosphodiesterase inhibitor, dipyridamole. The present invention describes novel (nitrosated/nitrosylated) phosphodiesterase inhibitors, and compns. contg. at least one (nitrosated/nitrosylated) phosphodiesterase inhibitor, and, optionally, one or more compds. that donate, transfer or release NO, elevate endogenous levels of endothelium-derived relaxing factor, stimulate endogenous synthesis of NO, or is a substrate for nitric oxide synthase and/or one or more vasoactive agents. The present invention also provides methods for treating or

preventing sexual dysfunctions in males and females, for enhancing sexual responses in males and females, and for treating or preventing diseases induced by the increased metab. of cGMP, such as hypertension, pulmonary hypertension, etc.

IT **150452-18-9P**, 1-[4-[(1,3-Benzodioxol-5-ylmethyl)amino]-6-chloro-2-quinazolinyl]-4-piperidine-carboxylic acid
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; synthesis of nitrosated and nitrosylated (hetero)cyclic phosphodiesterase inhibitors used in treatment of sexual dysfunction)

RN 150452-18-9 CAPLUS

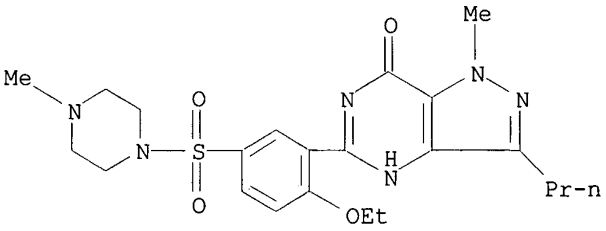
CN 4-Piperidinecarboxylic acid, 1-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-6-chloro-2-quinazolinyl]- (9CI) (CA INDEX NAME)



IT **139755-83-2D**, Sildenafil, nitroso derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis of nitrosated and nitrosylated (hetero)cyclic phosphodiesterase inhibitors used in treatment of sexual dysfunction)

RN 139755-83-2 CAPLUS

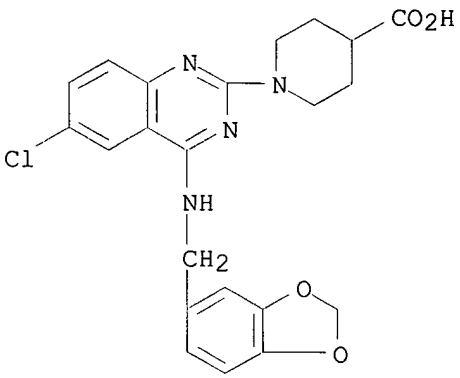
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



IT **150452-19-0D**, E 4021, nitroso derivs. **171596-29-5D**, ICOS 351, nitroso derivs.
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis of nitrosated and nitrosylated (hetero)cyclic phosphodiesterase inhibitors used in treatment of sexual dysfunction)

RN 150452-19-0 CAPLUS

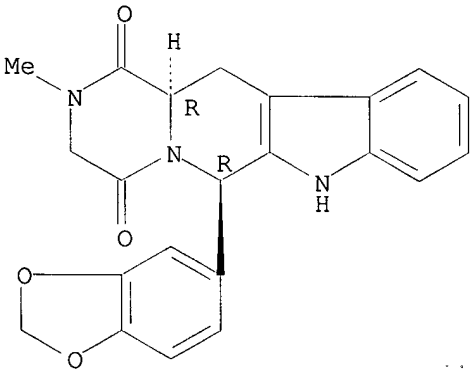
CN 4-Piperidinecarboxylic acid, 1-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-6-chloro-2-quinazolinyl]-, monosodium salt (9CI) (CA INDEX NAME)



● Na

RN 171596-29-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 86 THERE ARE 86 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

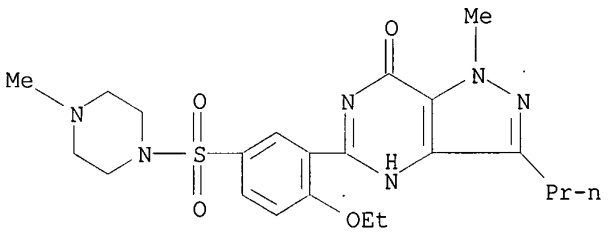
L46 ANSWER 4 OF 63 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 4
ACCESSION NUMBER: 2001:849912 CAPLUS
DOCUMENT NUMBER: 136:144966
TITLE: Transient renal effects of sildenafil in male kidney transplant recipients
AUTHOR(S): Malavaud, Bernard; Rostaing, Lionel; Tuan, Tran-Van; Tack, Ivan; Ader, Jean-Louis
CORPORATE SOURCE: Department of Urology and Renal Transplantation, Department of Nephrology, Dialysis, and Transplantation, Department of Physiology and INSERM Unit 388, Hopital Rangueil, Toulouse, Fr.
SOURCE: Transplantation (2001), 72(7), 1331-1333
CODEN: TRPLAU; ISSN: 0041-1337
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Sildenafil (Viagra) improves erection by sustaining Guanosine 3', 5'-cyclic monophosphate (cGMP)-mediated smooth muscle relaxation in the

corpus cavernosum. It also induces systemic vasodilation, resulting in a minor decrease in blood pressure. We evaluated the effect of one dose of sildenafil on graft function and hemodynamics in impotent male transplant recipients. Two sets of combined lithium, inulin, and p-amino hippurate clearance studies were conducted, with and without sildenafil (100 mg orally) in 11 male kidney transplant recipients (KTRs). Sildenafil increased glomerular filtration rate by 14.+-.4 from the baseline value of 55.+-.7 mL.cntdot.min-1.1.73 m2-1 (P<0.01), whereas calcd. renal **vascular resistances** decreased by 40.+-.18 from the baseline value of 247.+-.29 mmHg/L.cntdot.min-1.1.73 m2-1 (P<0.05). The oral administration of sildenafil in KTRs did not impair the function of the graft. In terms of renal physiol., the obsd. modifications did not warrant any specific precautions when offering sildenafil to KTRs suffering from erectile dysfunction.

IT **139755-83-2**, Sildenafil
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(transient renal effects of sildenafil in male kidney transplant recipients)

RN 139755-83-2 CAPLUS

CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 5 OF 63 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 5

ACCESSION NUMBER: 2001:749552 CAPLUS
DOCUMENT NUMBER: 136:32047
TITLE: Effect of inhaled iloprost plus oral sildenafil in patients with primary **pulmonary hypertension**
AUTHOR(S): Wilkens, Heinrike; Guth, Angelika; Konig, Jochem; Forestier, Nicole; Cremers, Bodo; Hennen, Benno; Bohm, Michael; Sybrecht, Gerhard W.
CORPORATE SOURCE: Medizinische Klinik und Polikinik, Univ. Saarlandes, Homburg/Saar, D-66421, Germany
SOURCE: Circulation (2001), 104(11), 1218-1222
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

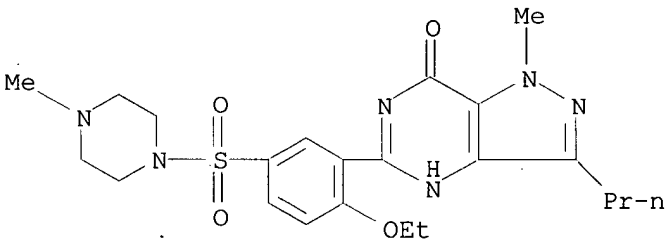
AB Background - The application of iloprost, a stable prostacyclin analog, by inhalation has been shown to improve hemodynamic variables in patients with primary pulmonary hypertension. However, repetitive inhalations are required due to its short-term effects. One potential approach to prolong and increase the vasorelaxant effects of aerosolized iloprost might be to combine use with phosphodiesterase inhibitors. Methods and Results - The short-term effects of 8.4 to 10.5 .mu.g of aerosolized iloprost, the phosphodiesterase type 5 inhibitor sildenafil, and the combination thereof

were compared in 5 patients with primary pulmonary hypertension. Aerosolized iloprost resulted in a more pronounced decrease in mean pulmonary arterial pressure (PAP) than sildenafil alone (9.4.+-.1.3 vs. 6.4.+-.1.1 mm Hg; P<0.05). The redn. in mean PAP after sildenafil was maximal after the first dose (25 mg). The combination of sildenafil plus iloprost lowered mean PAP significantly more than iloprost alone (13.8.+-.1.4 vs. 9.4.+-.1.3 mm Hg; P<0.009). No significant changes in heart rate or systemic arterial pressure were obsd. during any treatment. The treatments were well tolerated, without major adverse effects. Conclusions - Sildenafil caused a long-lasting redn. in mean PAP and pulmonary **vascular resistance**, with a further addnl. improvement after iloprost inhalation. These data suggest that small doses of a phosphodiesterase type 5 inhibitor may be a useful adjunct to inhaled iloprost in the management of pulmonary hypertension.

IT **139755-83-2**, Sildenafil
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of inhaled iloprost plus oral sildenafil in humans with primary **pulmonary hypertension**)

RN 139755-83-2 CAPLUS

CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 6 OF 63 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 6

ACCESSION NUMBER: 2001:720544 CAPLUS
DOCUMENT NUMBER: 136:31487
TITLE: Nebulized sildenafil is a selective **pulmonary** vasodilator in lambs with acute **pulmonary hypertension**
AUTHOR(S): Ichinose, Fumito; Erana-Garcia, Juan; Hromi, Jonathan; Raveh, Yehuda; Jones, Rosemary; Krim, Lori; Clark, Martin W. H.; Winkler, Jeffrey D.; Bloch, Kenneth D.; Zapol, Warren M.
CORPORATE SOURCE: Department of Anesthesia and Critical Care, Massachusetts General Hospital, Boston, MA, USA
SOURCE: Critical Care Medicine (2001), 29(5), 1000-1005
CODEN: CCMDC7; ISSN: 0090-3493
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

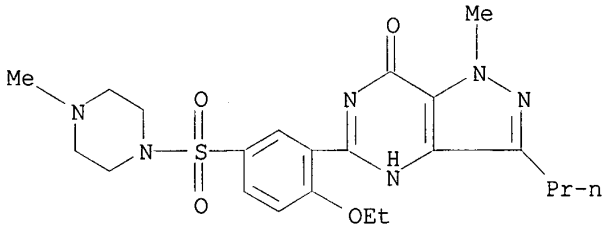
AB Objective: To det. whether inhalation of aerosolized sildenafil with and without inhaled nitric oxide (NO) causes selective pulmonary vasodilation in a sheep model of pulmonary hypertension. Design: A controlled lab. study in instrumented, awake, spontaneously breathing lambs. Setting: Animal research lab. affiliated with a university hospital. Subject: Twenty Suffolk lambs. Interventions: Lambs were instrumented with a carotid artery catheter, a pulmonary artery catheter, and a tracheostomy

tube and studied awake. After baseline measurements, pulmonary hypertension was induced by the continuous infusion of U46619, a thromboxane A2 analog. After breathing three concns. of inhaled NO (2, 5, and 20 ppm), lambs were divided into two groups. Group 1 (n = 7) breathed aerosols contg. 1, 10, and 30 mg of sildenafil alone, and group 2 (n = 4) simultaneously breathed NO (2 and 5 ppm) and aerosols contg. 10 mg of sildenafil. Hemodynamic measurements were obtained before and at the end of each drug administration. Venous admixt. was calcd., and plasma cGMP and sildenafil concns. were measured. Measurements and Main Results: Aerosols contg. 10 mg and 30 mg of sildenafil selectively decreased the pulmonary artery pressure by 21% .+-. 3% and 26% .+-. 3%, resp. ($p < .05$ vs. baseline pulmonary hypertension). When 10 mg of sildenafil was inhaled while simultaneously breathing 2 ppm and 5 ppm NO, the pulmonary artery pressure decreased by 35% .+-. 3% and 43% .+-. 2% ($p < .05$ vs. baseline pulmonary hypertension). Inhaled sildenafil did not impair systemic oxygenation, increase right-to-left intrapulmonary shunting, or impair the ability of inhaled NO to reduce right-to-left shunting. Conclusions: Nebulized sildenafil is a selective pulmonary vasodilator that can potentiate the pulmonary vasodilating effects of inhaled NO.

IT **139755-83-2**, Sildenafil
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nebulized sildenafil is selective **pulmonary** vasodilator that can potentiate effects of inhaled nitric oxide in lamb model of **pulmonary hypertension**)

RN 139755-83-2 CAPLUS

CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 7 OF 63 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 7
ACCESSION NUMBER: 2001:887438 CAPLUS
DOCUMENT NUMBER: 136:161309
TITLE: Cardiac electrophysiologic and hemodynamic effects of sildenafil, a PDE5 inhibitor, in anesthetized dogs
AUTHOR(S): Sugiyama, Atsushi; Satoh, Yoshioki; Shiina, Hiroyuki; Takahara, Akira; Yoneyama, Masahiko; Hashimoto, Keitaro
CORPORATE SOURCE: Department of Pharmacology, Yamanashi Medical University, Yamanashi, 409-3898, Japan
SOURCE: Journal of Cardiovascular Pharmacology (2001), 38(6), 940-946
CODEN: JCPCDT; ISSN: 0160-2446
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A recent in vitro study demonstrated that supratherapeutic concns. of sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor, blocked IKr and

prolonged cardiac repolarization. This study assessed the in vivo cardiohemodynamic and electrophysiol. effects of sildenafil using a halothane-anesthetized, closed-chest canine model (n = 5) to bridge the gap between basic observation and clin. experience. I.v. administration of sildenafil citrate in doses of 0.03, 0.3, and 3.0 mg/kg for 10 min, which provided sub- to supratherapeutic plasma drug concns., did not affect the monophasic action potential duration or effective refractory period of the right ventricle during the sinus rhythm as well as the ventricular pacing at the cycle length of 400 and 300 ms. However, sildenafil decreased the total peripheral resistance, simultaneously inducing pos. chronotropic and inotropic effects at the top dose, which gave plasma concns. at least 10 times higher than the therapeutic range. This cardiohemodynamic profile of sildenafil can be largely explained by reflex sympathetic activation assocd. with its vasodilator effect. Meanwhile, the lack of prolongation of the ventricular repolarization phase at the therapeutically relevant to moderately supratherapeutic sildenafil concns. supports the earlier clin. studies that indicate that sildenafil has no effect on ECG.

IT **171599-83-0**, Sildenafil citrate
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cardiac electrophysiol. and hemodynamic effects of sildenafil, a PDE5 inhibitor, in anesthetized dogs)

RN 171599-83-0 CAPLUS

CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) (9CI) (CA INDEX NAME)

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CRN 139755-83-2
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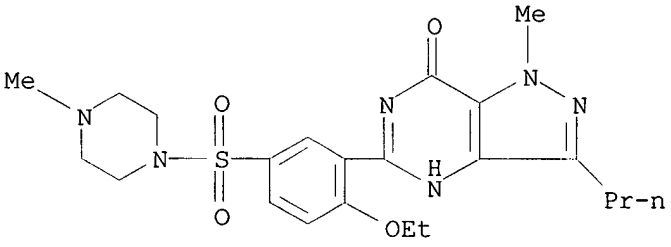
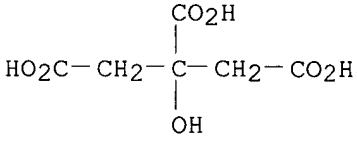


CM 2

CRN 77-92-9
CMF C6 H8 O7



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

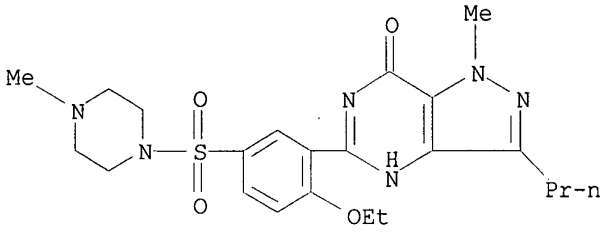
L46 ANSWER 8 OF 63 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 8

ACCESSION NUMBER: 2001:613877 CAPLUS
DOCUMENT NUMBER: 136:303788
TITLE: Sildenafil inhibits hypoxia-induced **pulmonary hypertension**
AUTHOR(S): Zhao, L.; Mason, N. A.; Morrell, N. W.; Kojonazarov, B.; Sadykov, A.; Maripov, A.; Mirrakhimov, M. M.; Aldashev, A.; Wilkins, M. R.
CORPORATE SOURCE: Section on Clinical Pharmacology, Imperial College School of Medicine, Hammersmith Hospital, London, W12 ONN, UK
SOURCE: Circulation (2001), 104(4), 424-428
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study investigated the effect of the phosphodiesterase 5 inhibitor sildenafil on the pulmonary vascular response to hypoxia in humans and mice. In a randomized, double-blind study, sildenafil 100 mg or placebo was given orally to 10 healthy volunteers 1 h before breathing 11% O2 for 30 min. Pulmonary artery pressure (PAP) was measured with an indwelling right heart catheter. The acute 56% increase in mean PAP produced by hypoxia during placebo treatment (mean PAP [mean mm Hg]: normoxia 16.0 vs. hypoxia 25.0) was almost abolished by sildenafil (normoxia 16.0 vs. hypoxia 18.0), with no significant effect on systemic blood pressure. In the isolated perfused lung of wild-type and endothelial NO synthase (eNOS)-deficient mice, sildenafil markedly blunted acute hypoxic pulmonary vasoconstriction. Wild-type mice dosed orally with the drug (25 mg .cntdot. kg-1 .cntdot. d-1) throughout 3 wk of exposure to hypoxia (10% O2) exhibited a significant redn. in right ventricular systolic pressure (placebo vs. sildenafil: 43.3 vs. 29.9 mm Hg) coupled with a small redn. in right ventricular hypertrophy and inhibition of pulmonary vascular remodeling. In eNOS mutant mice, sildenafil attenuated the increase in right ventricular systolic pressure but without a significant effect on right ventricular hypertrophy or vascular remodeling. Sildenafil attenuates hypoxia-induced pulmonary hypertension in humans and mice and offers a novel approach to the treatment of this condition. The eNOS-NO-cGMP pathway contributes to the response to sildenafil, but other biochem. sources of cGMP also play a role. Sildenafil has beneficial pulmonary hemodynamic effects even when eNOS activity is impaired.

IT **139755-83-2**, Sildenafil
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sildenafil inhibits hypoxia-induced **pulmonary hypertension**)

RN 139755-83-2 CAPLUS
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



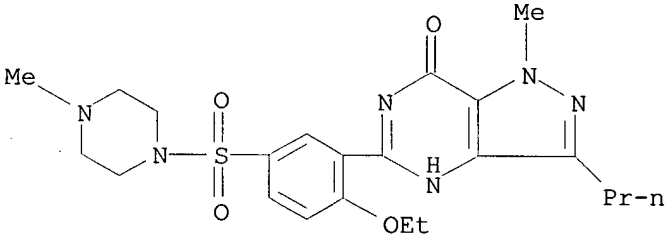
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Searched by Barb O'Bryen, STIC 308-4291

L46 ANSWER 9 OF 63 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 9
ACCESSION NUMBER: 2001:373554 CAPLUS
DOCUMENT NUMBER: 136:193916
TITLE: Sildenafil (Viagra) facilitates weaning of inhaled nitric oxide following placement of a biventricular-assist device
AUTHOR(S): Mychaskiw, G.; Sachdev, V.; Heath, B. J.
CORPORATE SOURCE: Department of Anesthesiology, University of Mississippi School of Medicine, Jackson, MS, USA
SOURCE: Journal of Clinical Anesthesia (2001), 13(3), 218-220
CODEN: JCLBE7; ISSN: 0952-8180
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Sildenafil is a selective phosphodiesterase type 5 inhibitor used in the treatment of erectile dysfunction. Here, the authors report the use of Sildenafil to blunt the rebound pulmonary hypertension seen following withdrawal of inhaled nitric oxide (NO) and Milrinone. The relatively long duration of Sildenafil's action on pulmonary artery pressures and lack of systemic hemodynamic effect make it an attractive option to facilitate weaning of inhaled NO.

IT **139755-83-2**, Sildenafil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Sildenafil facilitates weaning of inhaled nitric oxide after placement of biventricular-assist device)
RN 139755-83-2 CAPLUS
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 10 OF 63 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 10
ACCESSION NUMBER: 2000:445013 CAPLUS
DOCUMENT NUMBER: 133:276058
TITLE: Sildenafil is a **pulmonary** vasodilator in awake lambs with acute **pulmonary hypertension**
AUTHOR(S): Weimann, Jorg; Ullrich, Roman; Hromi, Jonathan; Fujino, Yuji; Clark, Martin W. H.; Bloch, Kenneth D.; Zapol, Warren M.
CORPORATE SOURCE: Department of Anesthesia and Critical Care, Harvard Medical School, Massachusetts General Hospital, Boston, MA, 02114, USA
SOURCE: Anesthesiology (2000), 92(6), 1702-1712
CODEN: ANESAV; ISSN: 0003-3022
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

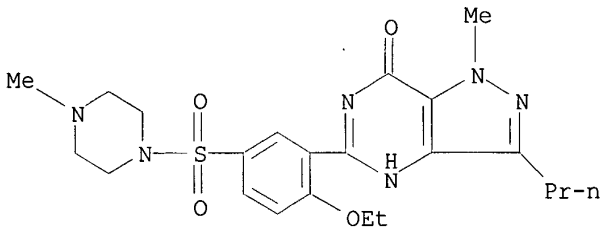
Searched by Barb O'Bryen, STIC 308-4291

AB Phosphodiesterase type 5 (PDE5) hydrolyzes cyclic guanosine monophosphate in the lung, thereby modulating NO/cGMP-mediated pulmonary vasodilation. Inhibitors of PDE5 were proposed for the treatment of pulmonary hypertension. In this study, the authors examd. the pulmonary and systemic vasodilator properties of sildenafil, a novel selective PDE5 inhibitor, which was approved for the treatment of erectile dysfunction. In an awake lamb model of acute pulmonary hypertension induced by an i.v. infusion of the thromboxane analog U46619, the authors measured the effects of 12.5, 25, and 50 mg sildenafil administered via a nasogastric tube on pulmonary and systemic hemodynamics (n=5). The authors also compared the effects of sildenafil (n=7) and zaprinast (n=5), a 2nd PDE5 inhibitor, on the pulmonary vasodilator effects of 2.5, 10, and 40 ppm inhaled NO. Finally, the authors examd. the effect of infusing i.v. L-NAME (an inhibitor of endogenous NO prodn.) on pulmonary vasodilation induced by 50 mg sildenafil (n=6). Cumulative doses of sildenafil (12.5, 25, and 50 mg) decreased the pulmonary artery pressure 21, 28, and 42%, resp., and the pulmonary **vascular resistance** 19, 23, and 45%, resp. Systemic arterial pressure decreased 12% only after the max. cumulative sildenafil dose. Neither sildenafil nor zaprinast augmented the ability of inhaled NO to dilate the pulmonary vasculature. Zaprinast, but not sildenafil, markedly prolonged the duration of pulmonary vasodilation after NO inhalation was discontinued. Infusion of L-NAME abolished sildenafil-induced pulmonary vasodilation. Sildenafil is a selective pulmonary vasodilator in an ovine model of acute pulmonary hypertension. Sildenafil induces pulmonary vasodilation via a NO-dependent mechanism. In contrast to zaprinast, sildenafil did not prolong the pulmonary vasodilator action of inhaled NO.

IT **139755-83-2**, Sildenafil
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(sildenafil is a pulmonary vasodilator)

RN 139755-83-2 CAPLUS

CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 11 OF 63 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:93121 CAPLUS
DOCUMENT NUMBER: 138:131173
TITLE: Use of 2-alkoxyphenyl-substituted imidazotriazinones
INVENTOR(S): Niewohner, Ulrich; Bischoff, Erwin; Haning, Helmut; Rahbar, Afssaneh; Bandel, Tiemo-Joerg; Barth, Wolfgang
PATENT ASSIGNEE(S): Bayer AG, Germany
SOURCE: Ger. Offen., 18 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German

Searched by Barb O'Bryen, STIC 308-4291

[redacted]

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10135815	A1	20030206	DE 2001-10135815	20010723
WO 2003011262	A2	20030213	WO 2002-EP7959	20020717

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

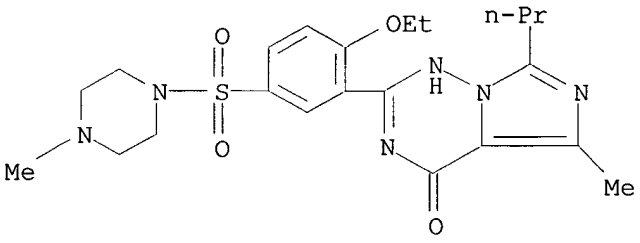
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: DE 2001-10135815 A 20010723
OTHER SOURCE(S): MARPAT 138:131173

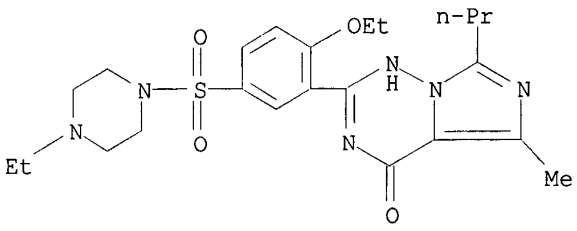
AB The invention discloses the use of known 2-phenyl-substituted imidazotriazinones with short, non-branched alkyl residues in the 9-Position and cyclic GMP phosphodiesterase-inhibitory characteristics for the prodn. of drugs for the treatment of heart failure, psoriasis, female infertility, cancer, diabetes, eye illnesses (e.g. glaucoma), disturbances of gastric mobility, cystic fibrosis, premature labor pains, pulmonary hypertension, bladder diseases, prostatic hyperplasia, nitrate-induced tolerance, preeclampsia, alopecia, Parkinson's disease, pain, tinnitus, or renal syndrome.

IT **224785-87-9 224785-90-4 224785-91-5**
224786-49-6 224789-15-5 330808-88-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(alkoxyphenyl-substituted imidazotriazinone cGMP phosphodiesterase inhibitors for therapeutic use)

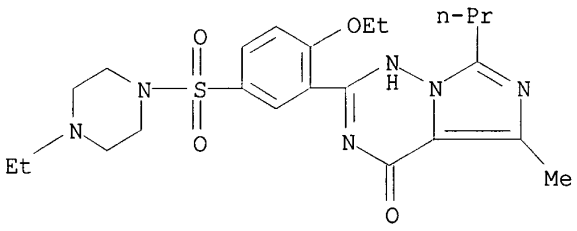
RN 224785-87-9 CAPLUS
CN Piperazine, 1-[[3-(1,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f][1,2,4]triazin-2-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



RN 224785-90-4 CAPLUS
CN Piperazine, 1-[[3-(1,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f][1,2,4]triazin-2-yl)-4-ethoxyphenyl]sulfonyl]-4-ethyl- (9CI) (CA INDEX NAME)

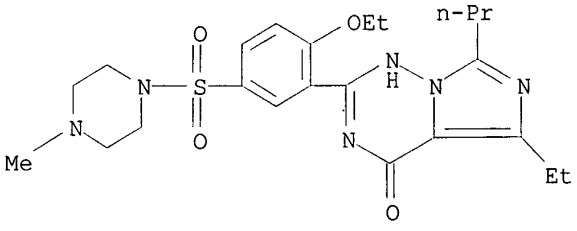


RN 224785-91-5 CAPLUS
CN Piperazine, 1-[[3-(1,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f][1,2,4]triazin-2-yl)-4-ethoxyphenyl]sulfonyl]-4-ethyl-, monohydrochloride (9CI) (CA INDEX NAME)

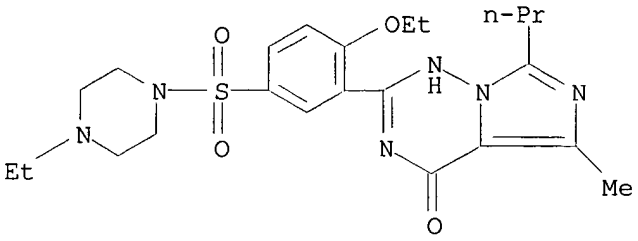


● HCl

RN 224786-49-6 CAPLUS
CN Piperazine, 1-[[4-ethoxy-3-(5-ethyl-1,4-dihydro-4-oxo-7-propylimidazo[5,1-f][1,2,4]triazin-2-yl)phenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)

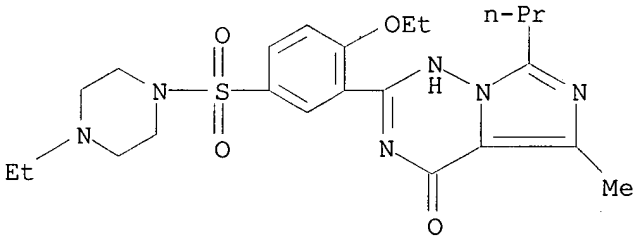


RN 224789-15-5 CAPLUS
CN Piperazine, 1-[[3-(1,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f][1,2,4]triazin-2-yl)-4-ethoxyphenyl]sulfonyl]-4-ethyl-, dihydrochloride (9CI) (CA INDEX NAME)



● 2 HCl

RN 330808-88-3 CAPLUS
CN Piperazine, 1-[[3-(1,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f][1,2,4]triazin-2-yl)-4-ethoxyphenyl]sulfonyl]-4-ethyl-, monohydrochloride, trihydrate (9CI) (CA INDEX NAME)



● HCl

● 3 H_2O

L46 ANSWER 12 OF 63 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:353456 CAPLUS
DOCUMENT NUMBER: 136:369739
TITLE: Preparation of pyrazino[1',2':1,6]pyrido[3,4-b]indole derivatives as phosphoesterase inhibitors for use as therapeutic agents
INVENTOR(S): Orme, Mark W.; Sawyer, Jason Scott; Schultze, Lisa M.
PATENT ASSIGNEE(S): Lilly Icos L.L.C., USA
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002036593	A1	20020510	WO 2001-US31364	20011009

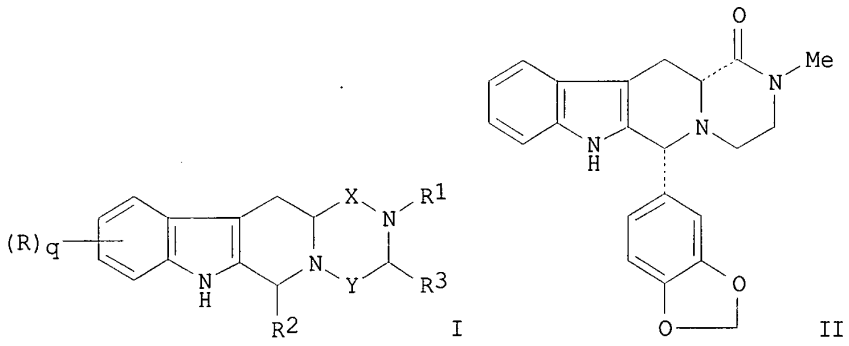
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL,
PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,
US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2002011493 A5 20020515 AU 2002-11493 20011009
PRIORITY APPLN. INFO.: US 2000-246257P P 20001106
WO 2001-US31364 W 20011009

OTHER SOURCE(S): MARPAT 136:369739

GI



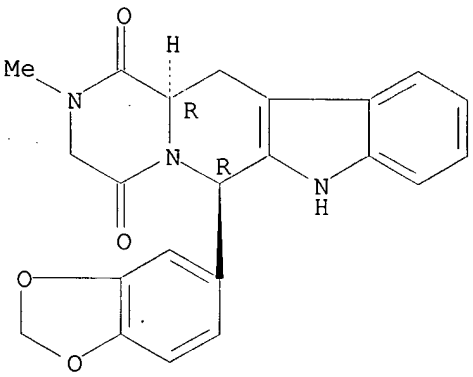
AB 2,3,6,7,12,12A-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole derivs., such as I [R = halo, alkyl; R1 = H, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heteroarylalkyl, etc.; R2 = monocyclic arom. ring, such as benzene, thiophene, furan, pyridine, etc.; R3 = H, alkyl; R1,R3 = fused carbocyclic ring; X, Y = CO, SO, SO2, CS, C(Ra)2; Ra = H, alkyl, benzyl; q = 0-4], pharmaceutically acceptable salts and solvates thereof, were prepd. for pharmaceutical use as phosphodiesterase inhibitors for the treatment of conditions, such as erectile dysfunction, female arousal disorder, angina, hypertension, and vascular disease. Thus, pyrazinopyridoindole deriv. II was prepd. by a multistep procedure starting with D-Tryptophan Me ester, piperonal and chloroacetaldehyde. The prepd. heterocycles were tested for phosphodiesterase V (PDE5) inhibitory activity with II exhibiting an IC50 of 54 nM.

IT **171596-29-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of pyrazino[1',2':1,6]pyrido[3,4-b]indole derivs. as phosphoesterase inhibitors for use as therapeutic agents)

RN 171596-29-5 CAPLUS

CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

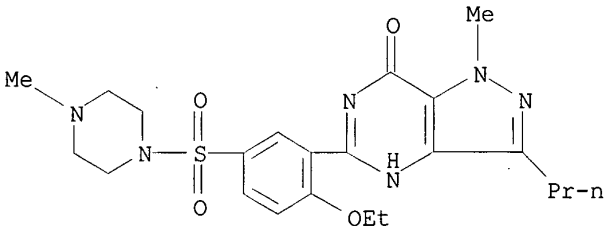
L46 ANSWER 13 OF 63 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:490376 CAPLUS
DOCUMENT NUMBER: 138:66430
TITLE: Sildenafil (Viagra) augments sodium nitroprusside-induced but not nitroglycerin-induced hypotension in dogs
AUTHOR(S): Yoo, Kyung Y.; Kim, Hak S.; Moon, Jai-Dong; Lee, JongUn
CORPORATE SOURCE: Department of Anesthesiology, Chonnam National University Medical School, Gwangju, S. Korea
SOURCE: Anesthesia & Analgesia (Baltimore, MD, United States) (2002), 94(6), 1505-1509
CODEN: AACRAT; ISSN: 0003-2999
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This work investigated whether sildenafil citrate (Viagra) may reduce the dose of nitro vasodilators required to induce deliberate hypotension. Dogs were instrumented with a femoral artery catheter and a pulmonary artery catheter. Sodium nitroprusside (SNP; 1-16 .mu.g/kg/min) or nitroglycerin (NTG; 2-32 .mu.g/kg/min) was given i.v. to induce hypotension. The animals were given either sildenafil pretreatment (1 mg/kg i.v. followed by 0.3 mg/kg/h) or no pretreatment (controls). Hemodynamic variables were continuously monitored. Plasma cGMP concns. were measured by RIA. Both SNP and NTG produced dose-dependent decreases in mean arterial blood pressure without affecting the heart rate, in the presence as well as in the absence of sildenafil. Systemic **vascular resistance** index and mean pulmonary arterial pressure also decreased. The magnitude of the redns. in mean arterial blood pressure and systemic **vascular resistance** caused by SNP was increased by sildenafil, whereas that caused by NTG was not affected. Neither SNP nor NTG alone altered plasma cGMP concns. Sildenafil increased the plasma cGMP concn., an action which was further increased by SNP but not affected by NTG. Sildenafil may reduce the dose of SNP required to produce hypotension in the dog. The potentiation of SNP-induced hypotension by sildenafil may be related to an increased accumulation of cGMP.

IT **139755-83-2**, Sildenafil **171599-83-0**, Viagra
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sildenafil citrate (Viagra) effect on sodium nitroprusside- and nitroglycerin-induced hypotension)

RN 139755-83-2 CAPLUS
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-

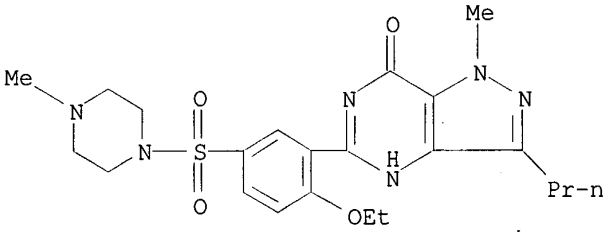
d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



RN 171599-83-0 CAPLUS
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) (9CI) (CA INDEX NAME)

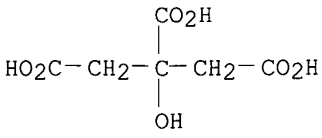
CM 1

CRN 139755-83-2
CMF C22 H30 N6 O4 S



CM 2

CRN 77-92-9
CMF C6 H8 O7



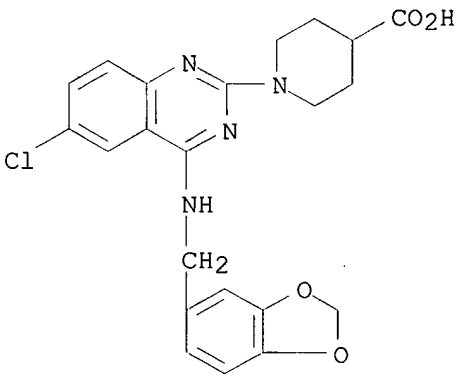
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 14 OF 63 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:322338 CAPLUS
DOCUMENT NUMBER: 137:345358
TITLE: Phosphodiesterase inhibitor
AUTHOR(S): Muramatsu, Masashi
CORPORATE SOURCE: Department of Respiratory Medicine, Juntendo University School of Medicine, Tokyo, 113-8421, Japan
SOURCE: Lung Perspectives (2002), 10(1), 65-70
CODEN: LUPEFF; ISSN: 0919-5742

Searched by Barb O'Bryen, STIC 308-4291

[redacted]

PUBLISHER: Medikaru Rebyusha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review, discussing the action mechanism and pharmacol. of selective phosphodiesterase-5 inhibitors, including E4021 and E4010 for treatment of acute and chronic pulmonary hypertension.
IT **150452-19-0**, E4021
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphodiesterase inhibitors for treatment of acute and chronic **pulmonary hypertension**)
RN 150452-19-0 CAPLUS
CN 4-Piperidinecarboxylic acid, 1-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-6-chloro-2-quinazolinyl]-, monosodium salt (9CI) (CA INDEX NAME)



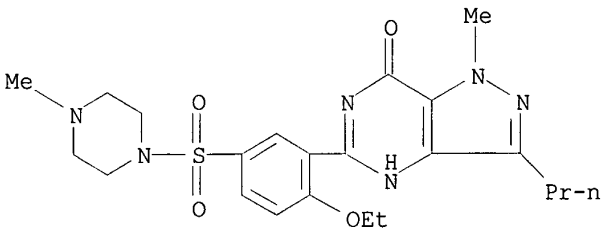
L46 ANSWER 15 OF 63 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:968675 CAPLUS
DOCUMENT NUMBER: 138:32692
TITLE: Phosphodiesterase type 5 inhibition in cardiovascular disease: experimental models and potential clinical applications
AUTHOR(S): Jackson, G.
CORPORATE SOURCE: Cardiac Department, Guy's and St. Thomas' Hospital, London, UK
SOURCE: European Heart Journal Supplements (2002), 4(Suppl. H), H19-H23
CODEN: EHJSFT; ISSN: 1520-765X
PUBLISHER: W. B. Saunders
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Inhibition of phosphodiesterase type 5, with amplification of the nitric oxide-cyclic nucleotide signalling pathway, and smooth muscle relaxation within erectile tissues and the penile vasculature, is the mechanism underlying the pro-erectile effects of sildenafil citrate. However, this enzyme is also expressed in other vascular beds, and preliminary findings have suggested that phosphodiesterase type 5 inhibition represents a promising treatment strategy for a range of cardiovascular conditions, including hypertension and chronic heart failure. Administered either alone or in concert with an inhaled prostacyclin analog, sildenafil exhibited beneficial vasodilator effects in patients with pulmonary hypertension, reducing pulmonary arterial

pressure and pulmonary **vascular resistance**, as well as prolonging exercise time and enhancing quality of life. Among patients with heart failure, sildenafil also significantly increased brachial artery diam. (vs. placebo) in a flow-mediated vasodilatation paradigm and augmented the blood pressure lowering effects of a calcium channel blocker in men with essential hypertension. Sildenafil was also well tolerated and/or increased the ischemic threshold during exercise testing in men with stable coronary heart disease. Concomitant therapy with sildenafil and nitrates or nitric oxide donors can cause profound hypotension (and other adverse effects), and is thus absolutely contraindicated.

IT **139755-83-2**, Sildenafil
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphodiesterase type 5 inhibition in cardiovascular disease)

RN 139755-83-2 CAPLUS

CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 16 OF 63 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:338071 CAPLUS
DOCUMENT NUMBER: 134:336223
TITLE: Treatment of **pulmonary hypertension** with sildenafil or other phosphodiesterase V inhibitor
INVENTOR(S): Butrous, Ghazwan Saleem; Lukas, Timothy; Machin, Ian
PATENT ASSIGNEE(S): Pfizer Limited, UK; Pfizer Inc.
SOURCE: Eur. Pat. Appl., 16 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1097711	A2	20010509	EP 2000-309212	20001101
EP 1097711	A3	20010801		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
ZA 2000006165	A	20020430	ZA 2000-6165	20001031
JP 2001172182	A2	20010626	JP 2000-335765	20001102

PRIORITY APPLN. INFO.: GB 1999-25970 A 19991102
GB 2000-3235 A 20000211

AB This invention relates to the use of certain cyclic guanosine 3',5'-monophosphate phosphodiesterase type 5 inhibitors, including in particular the compd. sildenafil, for the treatment of pulmonary hypertension.

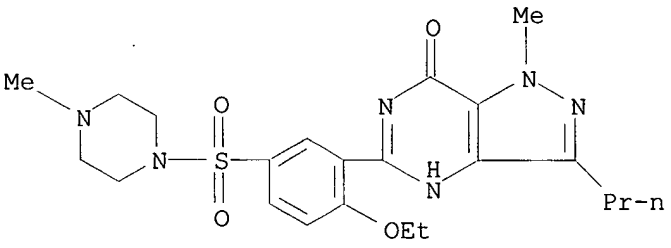
IT **139755-83-2**, Sildenafil

[redacted]

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(sildenafil or other phosphodiesterase V inhibitor for treatment of **pulmonary hypertension**)

RN 139755-83-2 CAPLUS

CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



IT **252959-28-7P**

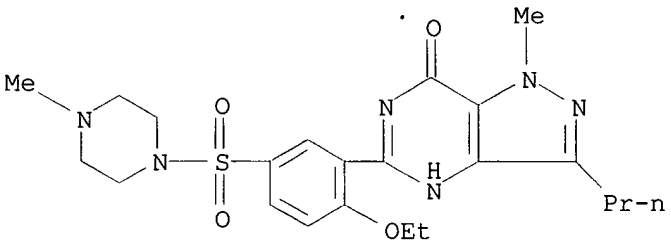
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(sildenafil or other phosphodiesterase V inhibitor for treatment of **pulmonary hypertension**)

RN 252959-28-7 CAPLUS

CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)

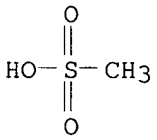
CM 1

CRN 139755-83-2
CMF C22 H30 N6 O4 S



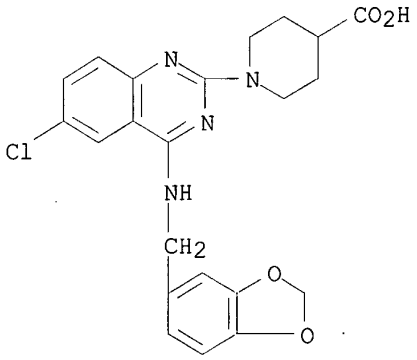
CM 2

CRN 75-75-2
CMF C H4 O3 S



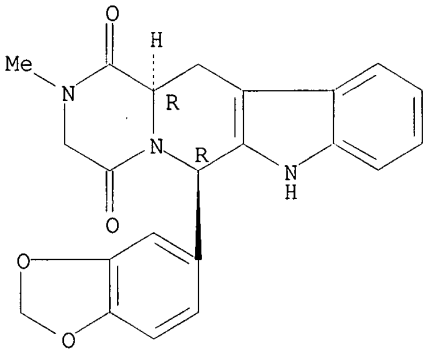
IT **150452-18-9 171596-29-5 171599-83-0,**
Sildenafil citrate **224785-90-4 252231-68-8**
252232-48-7
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sildenafil or other phosphodiesterase V inhibitor for treatment of **pulmonary hypertension**)

RN 150452-18-9 CAPLUS
CN 4-Piperidinecarboxylic acid, 1-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-6-chloro-2-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 171596-29-5 CAPLUS
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

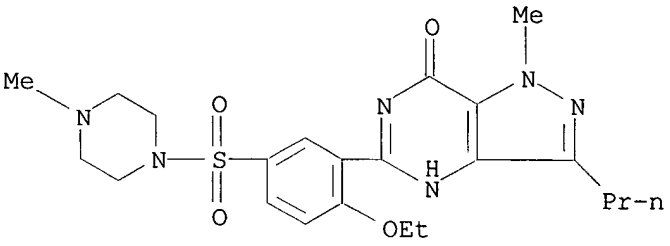
Absolute stereochemistry. Rotation (+).



RN 171599-83-0 CAPLUS
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) (9CI) (CA INDEX NAME)

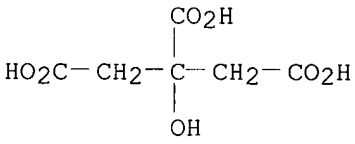
CM 1

CRN 139755-83-2
CMF C22 H30 N6 O4 S

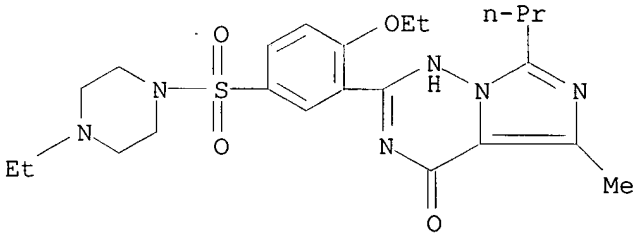


CM 2

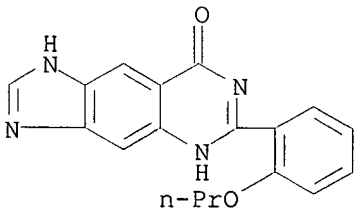
CRN 77-92-9
CMF C6 H8 O7



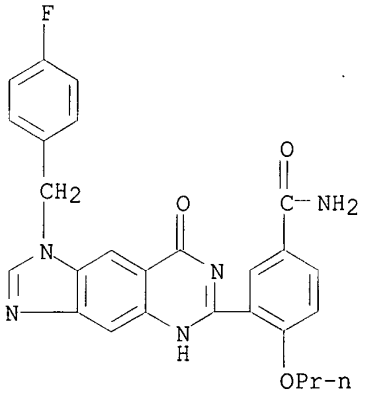
RN 224785-90-4 CAPLUS
CN Piperazine, 1-[[3-(1,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f][1,2,4]triazin-2-yl)-4-ethoxyphenyl]sulfonyl]-4-ethyl- (9CI) (CA INDEX NAME)



RN 252231-68-8 CAPLUS
CN 8H-Imidazo[4,5-g]quinazolin-8-one, 1,5-dihydro-6-(2-propoxyphenyl)- (9CI) (CA INDEX NAME)



RN 252232-48-7 CAPLUS
CN Benzamide, 3-[1-[(4-fluorophenyl)methyl]-5,8-dihydro-8-oxo-1H-imidazo[4,5-g]quinazolin-6-yl]-4-propoxy- (9CI) (CA INDEX NAME)



L46 ANSWER 17 OF 63 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:15013 CAPLUS
DOCUMENT NUMBER: 132:69341
TITLE: Nasal delivery of sildenafil citrate
INVENTOR(S): Romeo, Vincent D.; Behl, Charanjit R.
PATENT ASSIGNEE(S): Nastech Pharmaceutical Company, Inc., USA
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000000199	A1	20000106	WO 1999-US14352	19990624
W: AU, CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9947172	A1	20000117	AU 1999-47172	19990624

PRIORITY APPLN. INFO.: US 1998-90941P P 19980626
US 1998-90941 P 19980626
WO 1999-US14352 W 19990624

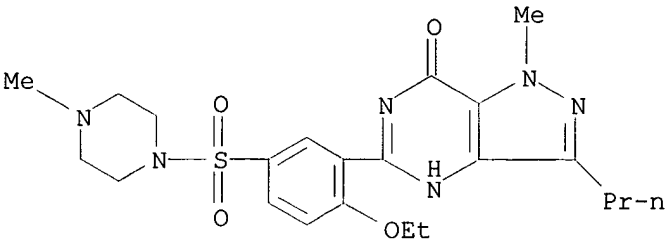
AB Intranasal dosage units of cyclic guanosine monophosphate-specific phosphodiesterase inhibitors are described which are combined with suitable intranasal carriers having a buffer, surfactants and absorption enhancers. The pH of the buffer and concn. of the surfactant are selected to facilitate absorption of the inhibitor across the nasal mucosa of a mammal in order to achieve a peak plasma concn. of the inhibitor in less than 1 h, and desirably within 30 min of administration.

IT **171599-83-0**, Sildenafil citrate
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nasal drugs contg. phosphodiesterase inhibitors and carriers and absorption enhancers)

RN 171599-83-0 CAPLUS
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) (9CI) (CA INDEX NAME)

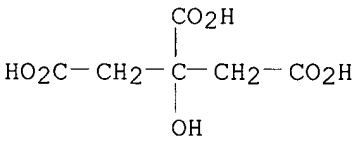
CM 1

CRN 139755-83-2
CMF C22 H30 N6 O4 S



CM 2

CRN 77-92-9
CMF C6 H8 O7



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 18 OF 63 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:23067 CAPLUS
DOCUMENT NUMBER: 135:70936
TITLE: Sympathetic activation by Sildenafil
AUTHOR(S): Phillips, Bradley G.; Kato, Masahiko; Pesek, Catherine A.; Winnicki, Mikolaj; Narkiewicz, Krzysztof; Davison, Diane; Somers, Virend K.
CORPORATE SOURCE: Division of Clinical and Administrative Pharmacy, University of Iowa, Iowa, USA
SOURCE: Circulation (2000), 102(25), 3068-3073
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

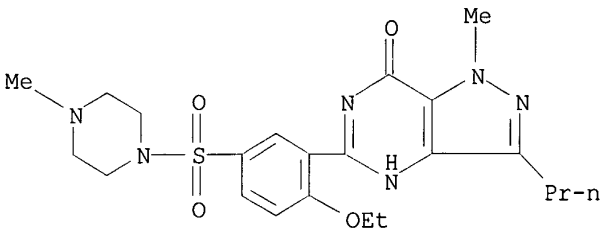
AB Sildenafil citrate is an effective and widely prescribed therapy for erectile dysfunction. Little is known about the effects of sildenafil on neural control of the circulation or about the effects of sildenafil on neurocirculatory stress responses. We studied 14 normal volunteers (age 32.+-.7 yr) who were randomized in a double-blind crossover fashion to receive a single oral dose of sildenafil 100 mg or placebo on 2 sep. study days. Blood pressure, heart rate, forearm **vascular resistance**, muscle sympathetic nerve activity, and plasma catecholamines were measured at baseline and at 30 and 60 min after sildenafil and after placebo administration. The effects of sildenafil and placebo on neural and circulatory responses to stressful stimuli (sustained handgrip, maximal forearm ischemia, mental stress, and the cold pressor test) were also evaluated. Blood pressure, heart rate, and forearm **vascular resistance** after sildenafil and placebo were similar. However, muscle sympathetic nerve activity increased strikingly after sildenafil (by 141.+-.26%, mean.+-.SEM) compared with placebo (3.+-.8%) (P=0.006); plasma norepinephrine levels also increased by 31.+-.5% after sildenafil administration (P=0.004). Sympathetic nerve traffic during mental, phys., and cold stresses was 2-

to 8-fold higher after sildenafil than with placebo (P<0.05). Sildenafil causes a marked increase in sympathetic activation, evident both at rest and during stressful stimuli. Sympathetic activation by sildenafil may have implications for understanding cardiovascular events assocd. with sildenafil use.

IT **139755-83-2**, Sildenafil
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effect of sildenafil on hemodynamics and sympathetic nerve traffic at rest and during stressful conditions)

RN 139755-83-2 CAPLUS

CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 19 OF 63 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:419299 CAPLUS
DOCUMENT NUMBER: 133:26805
TITLE: Hemodynamic effects of sildenafil in men with severe coronary artery disease
AUTHOR(S): Herrmann, Howard C.; Chang, Gene; Klugherz, Bruce D.; Mahoney, Paul D.
CORPORATE SOURCE: From the Cardiovascular Division, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, 19104, USA
SOURCE: New England Journal of Medicine (2000), 342(22), 1622-1626
CODEN: NEJMAG; ISSN: 0028-4793
PUBLISHER: Massachusetts Medical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: The cardiovascular effects of sildenafil are important because of the frequent presence of underlying cardiac disease in men with erectile dysfunction and reports indicating serious cardiac events temporally assocd. with the use of this drug. Methods: We assessed the systemic, pulmonary, and coronary hemodynamic effects of oral sildenafil (100 mg) in 14 men (mean [.+-.SD] age, 61.+-.11 yr) with severe stenosis of at least one coronary artery (stenosis of >70 % of the vessel diam.) who were scheduled to undergo percutaneous coronary revascularization. Blood-flow velocity and flow reserve were assessed with a Doppler guidewire in 25 coronary arteries, including 13 severely diseased arteries (mean degree of stenosis, 78.+-.7 %) and 12 arteries without stenosis, used as a ref.; maximal hyperemia was induced (to assess flow reserve) with the intracoronary administration of adenosine both before and after sildenafil. Results: Oral sildenafil produced only small decreases (<10 %) in systemic arterial and pulmonary arterial pressures, and it had no effect on pulmonary-capillary wedge pressure, right atrial pressure, heart rate, or cardiac output. There were no significant changes in av. peak

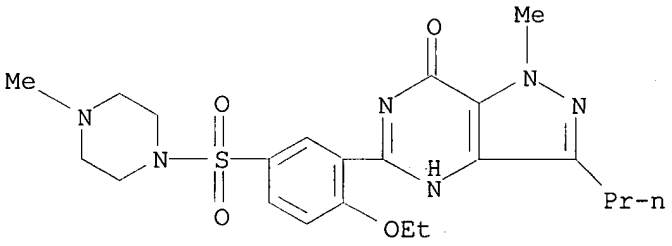
[redacted]

coronary flow velocity, coronary-artery diam., volumetric coronary blood flow, or coronary **vascular resistance**. Coronary flow reserve at base line was lower in the stenosed arteries (1.26.+-.0.26) than in the ref. arteries (2.19.+-.0.44) and increased about 13 % in both groups of arteries combined after the administration of sildenafil (from 1.70.+-.0.59 to 1.92.+-.0.72, P=0.003). The ratio of coronary flow reserve in coronary arteries with stenosis to that in the ref. arteries (0.57.+-.0.14) was not affected by sildenafil. Conclusions: No adverse cardiovascular effects of oral sildenafil were detected in men with severe coronary artery disease.

IT **139755-83-2**, Sildenafil
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hemodynamic effects of sildenafil in men with severe coronary artery disease)

RN 139755-83-2 CAPLUS

CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 20 OF 63 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:251429 CAPLUS
DOCUMENT NUMBER: 131:53795
TITLE: E4021, a selective phosphodiesterase 5 inhibitor, potentiates the vasodilator effect of inhaled nitric oxide in isolated perfused rat lungs
AUTHOR(S): Ohnishi, Masahiro; Oka, Masahiko; Muramatsu, Masashi; Sato, Koichi; Kira, Shiro; Fukuchi, Yoshinosuke
CORPORATE SOURCE: Department of Respiratory Medicine, Juntendo University School of Medicine, Tokyo, 113, Japan
SOURCE: Journal of Cardiovascular Pharmacology (1999), 33(4), 619-624
CODEN: JCPCDT; ISSN: 0160-2446
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

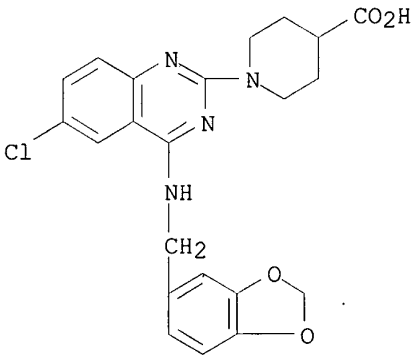
AB To test whether E4021, a potent selective cGMP phosphodiesterase inhibitor, causes pulmonary vasodilation and whether it enhances the vasodilator action of inhaled nitric oxide (NO), we studied its effects on pulmonary vascular tone and inhaled NO-induced pulmonary vasodilation in isolated perfused rat lungs. Lungs were perfused at a const. flow rate with salt-Ficoll soln. and ventilated with air plus 5% CO2. After equilibration, vasodilator responses to either E4021, inhaled NO, or both were evaluated under conditions of increased perfusion pressure induced by infusion of U46619. E4021 had no effect on the baseline perfusion pressure, whereas it caused dose-dependent pulmonary vasodilation when the vasomotor tone was increased by U46619. Inhaled 1, 5, and 20 ppm NO reduced the increased perfusion pressure by 60.+-.5%, 83.+-.3%, and

92.+-.2%, resp. Pretreatment with E4021 significantly potentiated the vasodilator effect of 1 ppm NO (from 53.+-.6% to 71.+-.2%; $p < 0.05$) but did not alter that of 5 ppm NO (from 77.+-.3% to 78.+-.4%; $p > 0.05$). In addn., pretreatment with E4021 significantly augmented the vasodilator response to sodium nitroprusside but not to isoproterenol. These results indicate that E4021 causes pulmonary vasodilation and potentiates the vasodilator effect of low concns. of inhaled NO, probably through a cGMP-dependent mechanism in salt-soln. perfused rat lungs. We conclude that E4021 may possibly be useful for the treatment of pulmonary hypertension, either alone or in combination with inhaled NO.

IT **150452-19-0**, E4021
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(E4021, a selective phosphodiesterase 5 inhibitor, potentiates vasodilator effect of inhaled nitric oxide in isolated perfused rat lungs)

RN 150452-19-0 CAPLUS

CN 4-Piperidinecarboxylic acid, 1-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-6-chloro-2-quinazolinyl]-, monosodium salt (9CI) (CA INDEX NAME)



Compound d

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 21 OF 63 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:211458 CAPLUS
DOCUMENT NUMBER: 130:276484
TITLE: Effects of sildenafil citrate on human hemodynamics
AUTHOR(S): Jackson, Graham; Benjamin, Nigel; Jackson, Neville; Allen, Michael J.
CORPORATE SOURCE: Guys and St. Thomas Hospital, London, SE1 7EH, UK
SOURCE: American Journal of Cardiology (1999), 83(5A), 13C-20C
CODEN: AJCDAG; ISSN: 0002-9149
PUBLISHER: Excerpta Medica, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Nitric oxide (NO) induces the formation of intracellular cGMP (cGMP) by guanylate cyclase. Sildenafil, which selectively inhibits phosphodiesterase type 5 (PDE5) found predominantly in the corpora cavernosa of the penis, effectively blocks the degrdn. of cGMP and enhances erectile function in men with erectile dysfunction. The NO-cGMP pathway also plays an important role in mediating blood pressure. It is,

therefore, possible that the therapeutic doses of sildenafil used to treat erectile dysfunction may have clin. significant effects on human hemodynamics. Three studies were undertaken to assess the effects of i.v., intra-arterially, and orally administered doses of sildenafil on blood pressure, heart rate, cardiac output, and forearm blood flow and venous compliance in healthy men. A fourth study evaluated the hemodynamic effects of i.v. sildenafil in men with stable ischemic heart disease. In healthy men, significant ($p < 0.01$) decreases in supine systolic and diastolic blood pressures were obsd. with i.v. sildenafil (20, 40, and 80 mg) at the end of the infusion period when plasma levels of sildenafil were highest (mean decreases from baseline of 7.0/6.9 and 9.2/6.7 mm Hg, for the 40- and 80-mg doses, resp.). These changes were transient and not dose related. Modest redns. in systemic **vascular resistance** also were obsd. (max. decrease 16%), although heart rate was not affected by sildenafil administration when compared with placebo. Single oral doses of sildenafil (100, 150, and 200 mg) produced no significant changes in cardiac index from 1-12 h postdose between placebo- and sildenafil-treated subjects. The approved dosage strengths of sildenafil citrate are 25 mg, 50 mg, and 100 mg. The 80-mg i.v. dose and the 200-mg oral dose of sildenafil produced comparable plasma levels at twice the max. therapeutic dose (recommended range, 25-100 mg). After brachial artery infusion of sildenafil (up to 300 .mu.g/min), there was a modest vasodilation of resistance arteries and a reversal of norepinephrine-induced preconstriction of forearm veins. These hemodynamic effects were similar to but smaller in magnitude than those of nitrates. In a small pilot study of men with ischemic heart disease, decreases from baseline in pulmonary arterial pressure (-27% at rest and -19% during exercise) and cardiac output (-7% at rest and -11% during exercise) were obsd. after 40-mg i.v. doses of sildenafil. Sildenafil was well tolerated by subjects and patients in all studies, with headache and other symptoms of vasodilation the most commonly reported adverse effects of treatment. Modest, transient hemodynamic changes were obsd. in healthy men after single i.v. or oral doses of sildenafil even at supratherapeutic doses. In men with stable ischemic heart disease, sildenafil produced modest effects on hemodynamic parameters at rest and during exercise.

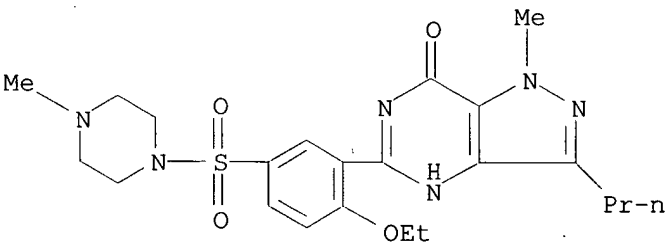
IT **171599-83-0**, Sildenafil citrate
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(sildenafil citrate effect on human hemodynamics)

RN 171599-83-0 CAPLUS

CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) (9CI) (CA INDEX NAME)

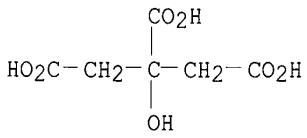
CM 1

CRN 139755-83-2
CMF C22 H30 N6 O4 S



CM 2

CRN 77-92-9
CMF C6 H8 O7

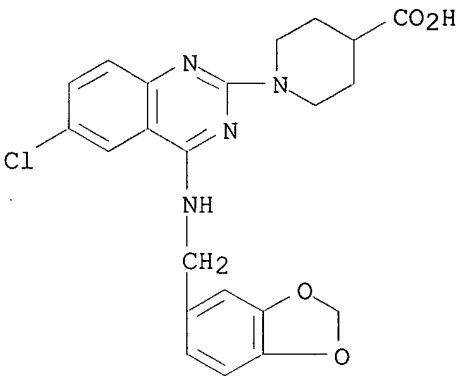


REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L46 ANSWER 22 OF 63 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:365277 CAPLUS
DOCUMENT NUMBER: 129:23196
TITLE: Type V phosphodiesterase inhibition modulates endogenous immunoreactivities of endothelin-1 and endothelial nitric oxide synthase in **pulmonary** arteries in rats with monocrotaline-induced **pulmonary hypertension**
AUTHOR(S): Takahashi, Takashi; Kanda, Tsugiyasu; Sumino, Hiroyuki; Inoue, Masahiro; Sato, Kunio; Sakamaki, Tetsuo; Kobayashi, Isao; Iwamoto, Aikichi; Nagai, Ryozo
CORPORATE SOURCE: Dep. Infectious Diseases Applied Immunology, Inst. Medical Sci., Univ. Tokyo, Tokyo, 108, Japan
SOURCE: Research in Experimental Medicine (1998), 197(6), 319-328
CODEN: REXMAS; ISSN: 0300-9130
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of oral administration of E4021 (100 mg/kg/day), a type V phosphodiesterase inhibitor, was evaluated on immunoreactivities of endothelin-1, endothelin receptors, and NO synthases in pulmonary arteries in a rat model of pulmonary hypertension. In rats treated with E4021, immunoreactivities of endothelin and endothelial NO synthase, redn. of right ventricular overload and medial thickening were obsd. less frequently than in controls treated with monocrotaline on day 28. The levels of blood plasma endothelin-1 and blood serum -NO3 and -NO2 were lower in rats that received E4021 than in the control with monocrotaline. Oral administration of E4021 modulated endogenous immunoreactivities of endothelin-1 and endothelial NO synthase with the improvement of right ventricular overload and medial thickening.

IT **150452-19-0**, E4021
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects on immunoreactivities of endothelin-1, endothelin receptors, and NO synthases in **pulmonary hypertension**)
RN 150452-19-0 CAPLUS
CN 4-Piperidinecarboxylic acid, 1-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-6-chloro-2-quinazolinyl]-, monosodium salt (9CI) (CA INDEX NAME)



● Na

L46 ANSWER 23 OF 63 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:303030 CAPLUS
DOCUMENT NUMBER: 126:282836
TITLE: Chloroquinazoline derivative compositions with improved bioavailability
INVENTOR(S): Kato, Akyoshi; Yoshiba, Takako; Yamakawa, Ichiro; Ando, Eishin
PATENT ASSIGNEE(S): Eisai Co Ltd, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 5 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

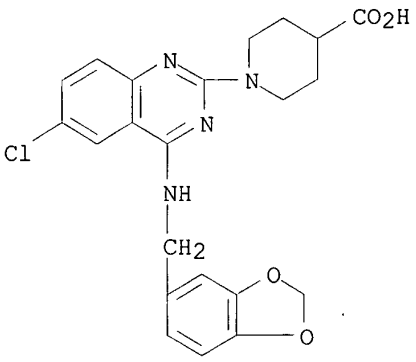
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 09059159	A2	19970304	JP 1995-216329	19950824

PRIORITY APPLN. INFO.: JP 1995-216329 19950824

AB The title compns. are manufd. by dissolving 2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline Na salt (I) and high-mol. wt. substances in EtOH (and H2O), then removing the solvent(s). Granules contg. I and high-mol. wt. substances are also claimed. I is useful for treatment of chronic heart failure and pulmonary hypertension (no data). Hydroxypropylcellulose acetate phthalate (5 g) was mixed with 1 g I in aq. EtOH, then evapd. to give a compn., which showed better soly. in artificial intestinal juice.

IT **150452-19-0**
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(6-chloroquinazoline deriv. compns. with improved bioavailability for treatment of heart failure and **pulmonary hypertension**
)

RN 150452-19-0 CAPLUS
CN 4-Piperidinecarboxylic acid, 1-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-6-chloro-2-quinazolinyl]-, monosodium salt (9CI) (CA INDEX NAME)

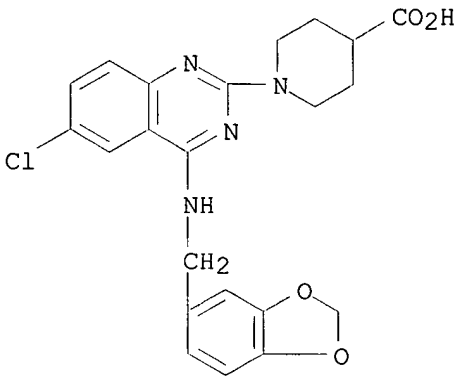


● Na

L46 ANSWER 24 OF 63 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:702723 CAPLUS
DOCUMENT NUMBER: 126:14503
TITLE: A selective type V phosphodiesterase inhibitor, E4021, protects [against] the development of right ventricular overload and medial thickening of **pulmonary** arteries in a rat model of **pulmonary hypertension**
AUTHOR(S): Takahashi, Takashi; Kanda, Tsugiyasu; Inoue, Masahiro; Suzuki, Tadashi; Kobayashi, Isao; Kodama, Kohtarou; Nagai, Ryozo
CORPORATE SOURCE: Second Department Internal Medicine, Gunma University School medicine, Maebashi, 371, Japan
SOURCE: Life Sciences (1996), 59(23), PL371-PL377
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of oral administration of E4021, a type V phosphodiesterase inhibitor (10, 30, and 100 mg/kg/day), on development of monocrotaline-induced right ventricular overload and medial thickening of pulmonary arteries were studied in rats. Right ventricular systolic pressure, the ratio right/left ventricular mass, right ventricular wall thickness, right ventricular myocardial fiber diam., and the medial thickness and smooth muscle area in pulmonary arteries were less after 28 days in rats that received E4021 at 30 and 100 mg/kg/day than in controls given monocrotaline only. Myofiber diam., medial thickness, and smooth muscle area were lower in rats treated with E4021 at 100 mg/kg/day than in those receiving 30 mg/kg/day. E4021 at 100 mg/kg/day protected against the development of right ventricular overload and medial thickening of pulmonary arteries.

IT **150452-19-0**, E 4021
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(heart overload and **pulmonary hypertension** inhibition by)
RN 150452-19-0 CAPLUS
CN 4-Piperidinecarboxylic acid, 1-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-6-chloro-2-quinazolinyl]-, monosodium salt (9CI) (CA INDEX NAME)



● Na

L46 ANSWER 25 OF 63 USPATFULL
ACCESSION NUMBER: 2003:31136 USPATFULL
TITLE: Nitrosated and nitrosylated phosphodiesterase inhibitors, compositions and methods of use
INVENTOR(S): Garvey, David S., Dover, MA, UNITED STATES
De Tejada, Inigo Saenz, Madrid, SPAIN
Earl, Richard A., Westford, MA, UNITED STATES
Khanapure, Subhash P., Clinton, MA, UNITED STATES

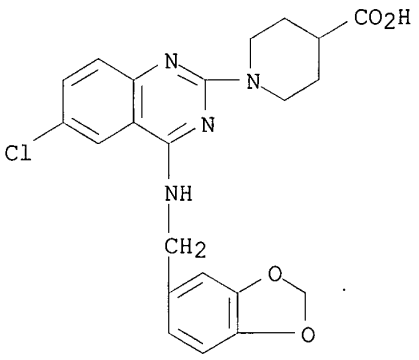
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003023087	A1	20030130
APPLICATION INFO.:	US 2002-216886	A1	20020813 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 2001-941691, filed on 30 Aug 2001, GRANTED, Pat. No. US 6462044 Continuation of Ser. No. US 1999-387727, filed on 1 Sep 1999, GRANTED, Pat. No. US 6331543 Continuation-in-part of Ser. No. US 1998-145142, filed on 1 Sep 1998, GRANTED, Pat. No. US 5958926 Continuation-in-part of Ser. No. US 1996-740764, filed on 1 Nov 1996, GRANTED, Pat. No. US 5874437 Continuation-in-part of Ser. No. WO 1997-US19870, filed on 31 Oct 1997, PENDING
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: EDWARD D GRIEFF, HALE & DORR LLP, 1455 PENNSYLVANIA AVE, NW, WASHINGTON, DC, 20004
NUMBER OF CLAIMS: 71
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 60 Drawing Page(s)
LINE COUNT: 4108
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention describes novel nitrosated and/or nitrosylated phosphodiesterase inhibitors, and novel compositions containing at least one nitrosated and/or nitrosylated phosphodiesterase inhibitor, and, optionally, one or more compounds that donate, transfer or release nitric oxide, elevate endogenous levels of endothelium-derived relaxing factor, stimulate endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase and/or one or more vasoactive agents. The present invention also provides novel compositions containing at least one phosphodiesterase inhibitor, and one or more compounds that donate, transfer or release nitric oxide, elevate endogenous levels of

endothelium-derived relaxing factor, stimulate endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase and/or one or more vasoactive agents. The present invention also provides methods for treating or preventing sexual dysfunctions in males and females, for enhancing sexual responses in males and females, and for treating or preventing diseases induced by the increased metabolism of cyclic guanosine 3',5'-monophosphate (cGMP), such as **hypertension**, **pulmonary hypertension**, congestive heart failure, renal failure, myocardial infraction, stable, unstable and variant (Prinzmetal) angina, atherosclerosis, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, stroke, asthma, bronchitis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, dementia, immunodeficiency, premature labor, dysmenorrhoea, benign prostatic hyperplasis (BPH), bladder outlet obstruction, incontinence, conditions of reduced blood vessel patency, e.g., postpercutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, allergic rhinitis, glucoma, and diseases characterized by disorders of gut motility, e.g., irritable bowel syndrome (IBS).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **150452-18-9P**, 1-[4-[[(1,3-Benzodioxol-5-yl)methyl]amino]-6-chloro-2-quinazolinyl]-4-piperidinecarboxylic acid
(intermediate; prepn. and uses of nitrosated and nitrosylated phosphodiesterase inhibitors)
RN 150452-18-9 USPATFULL
CN 4-Piperidinecarboxylic acid, 1-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-6-chloro-2-quinazolinyl]- (9CI) (CA INDEX NAME)



L46 ANSWER 26 OF 63 USPATFULL
ACCESSION NUMBER: 2002:221833 USPATFULL
TITLE: Tetracyclic derivatives, process of preparation and use
INVENTOR(S): Daugan, Alain Claude-Marie, Les Ulis, FRANCE
PATENT ASSIGNEE(S): ICOS Corporation (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002119976	A1	20020829
APPLICATION INFO.:	US 2002-68114	A1	20020205 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-633431, filed on 7 Aug 2000, PATENTED Continuation of Ser. No. US 1999-399667, filed on 21 Sep 1999, PATENTED Continuation of Ser. No. US 1998-133078, filed on 12 Aug 1998, PATENTED Division of Ser. No. US 1996-669389, filed on 16 Jul 1996, PATENTED

Searched by Barb O'Bryen, STIC 308-4291

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1994-1090	19940121
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	MARSHALL, GERSTEIN & BORUN, 6300 SEARS TOWER, 233 SOUTH WACKER, CHICAGO, IL, 60606-6357	
NUMBER OF CLAIMS:	17	
EXEMPLARY CLAIM:	1	
LINE COUNT:	2766	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A compound of formula (I) ##STR1##

and salts and solvates thereof, in which:

R.sup.o represents hydrogen, halogen or C.sub.1-6 alkyl;

R.sup.1 represents hydrogen, C.sub.1-6alkyl, C.sub.2-6alkenyl, C.sub.2-6 alkynyl, halo C.sub.1-6alkyl, C.sub.3-8cycloalkyl, C.sub.3-8cycloalkyl C.sub.1-3alkyl, arylC.sub.1-3alkyl or heteroaryl C.sub.1-3alkyl;

R.sup.2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring ##STR2##

attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen; and

R.sup.3 represents hydrogen or C.sub.1-3 alkyl, or R.sup.1 and R.sup.3 together represent a 3- or 4-membered alkyl or alkenyl chain.

A compound of formula (I) is a potent and'selective inhibitor of cyclic guanosine 3', 5'-monophosphate specific phosphodiesterase (CGMP specific PDE) having a utility in a variety of therapeutic areas where such inhibition is beneficial, including the treatment of cardiovascular disorders.

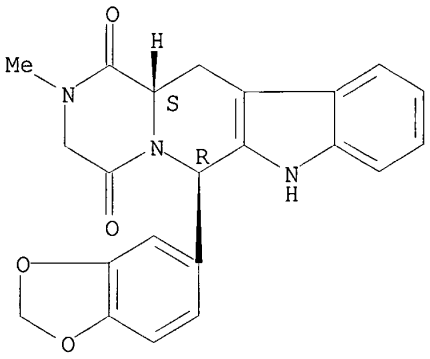
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **171488-01-0P 171488-03-2P 171488-04-3P**
171488-06-5P 171488-07-6P 171488-08-7P
171488-09-8P 171488-10-1P 171488-11-2P
171488-12-3P 171488-13-4P 171488-14-5P
171488-15-6P 171488-16-7P 171488-17-8P
171488-18-9P 171488-19-0P 171488-20-3P
171488-21-4P 171488-22-5P 171488-76-9P
171488-77-0P 171488-86-1P 171488-87-2P
171488-91-8P 171488-92-9P 171488-93-0P
171488-94-1P 171488-95-2P 171489-01-3P
171489-02-4P 171596-27-3P 171596-28-4P
171596-29-5P 171596-30-8P 171596-31-9P
171596-32-0P 171596-36-4P 171596-39-7P
171596-40-0P
(prepn. of pyrazinopyridoindolediones as inhibitors of cyclic guanosine monophosphate specific phosphodiesterase)

RN 171488-01-0 USPATFULL

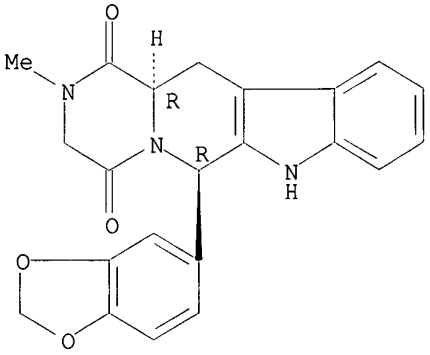
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



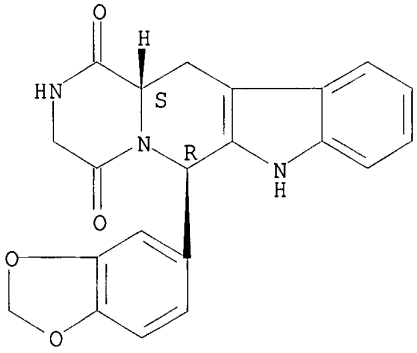
RN 171488-03-2 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



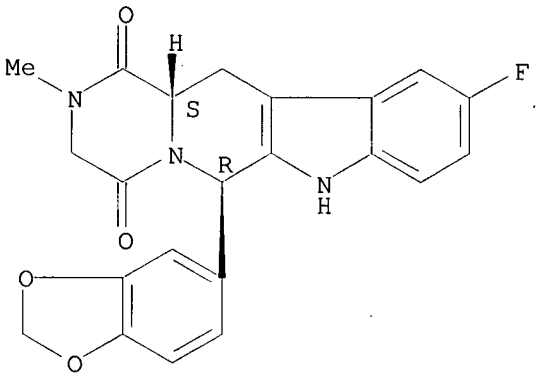
RN 171488-04-3 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



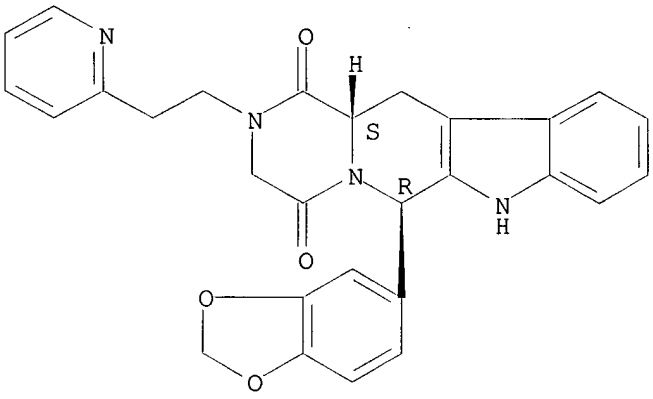
RN 171488-06-5 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-10-fluoro-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



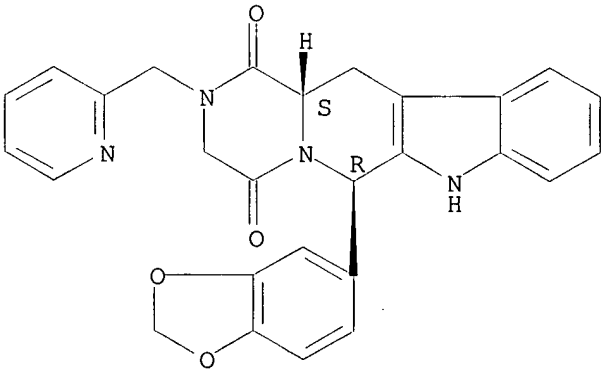
RN 171488-07-6 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[2-(2-pyridinyl)ethyl]-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



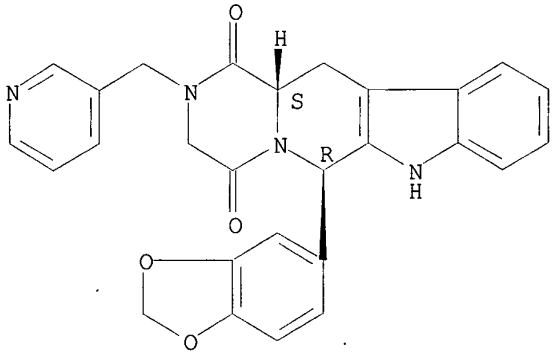
RN 171488-08-7 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-pyridinylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



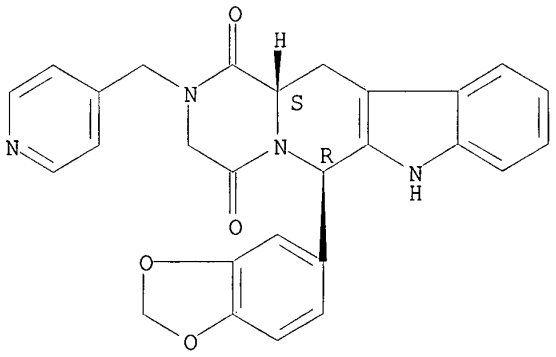
RN 171488-09-8 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(3-pyridinylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



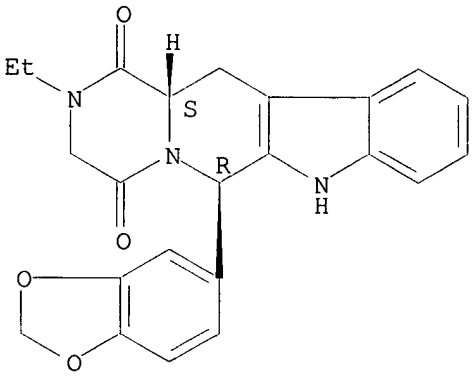
RN 171488-10-1 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(4-pyridinylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



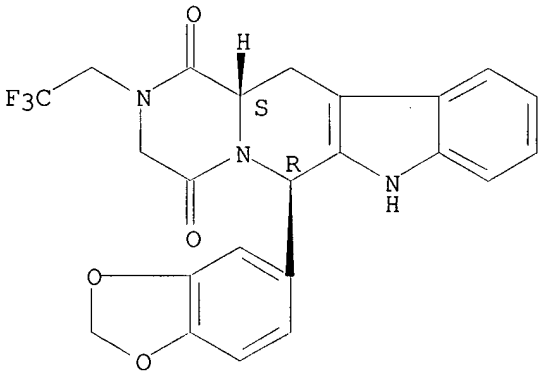
RN 171488-11-2 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-ethyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



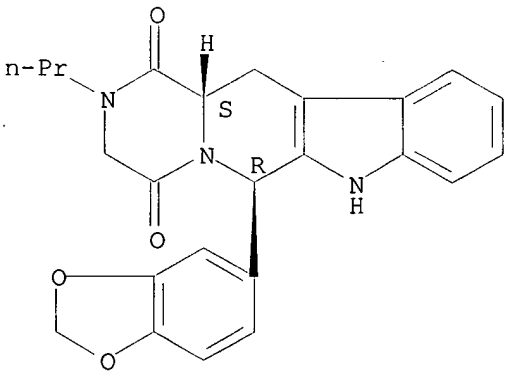
RN 171488-12-3 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2,2,2-trifluoroethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 171488-13-4 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-propyl-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

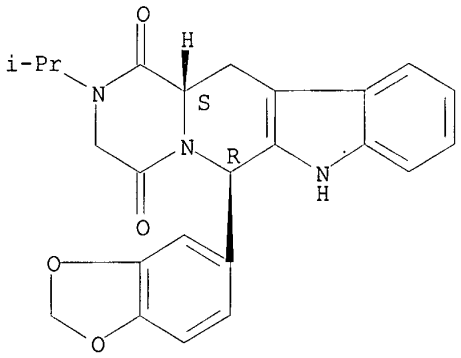
Relative stereochemistry.



RN 171488-14-5 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(1-methylethyl)-, (6R,12aS)-rel- (9CI) (CA

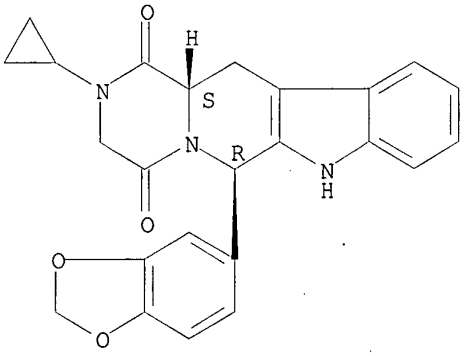
INDEX NAME)

Relative stereochemistry.



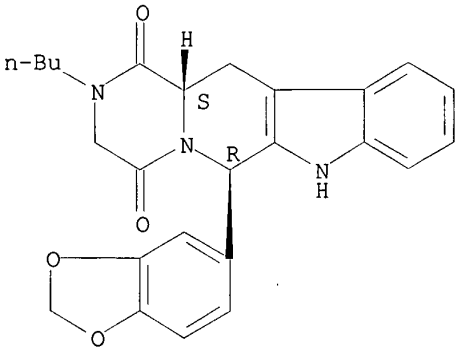
RN 171488-15-6 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclopropyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 171488-16-7 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-butyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

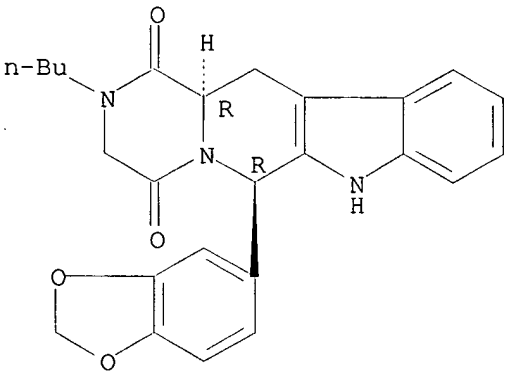
Relative stereochemistry.



RN 171488-17-8 USPATFULL

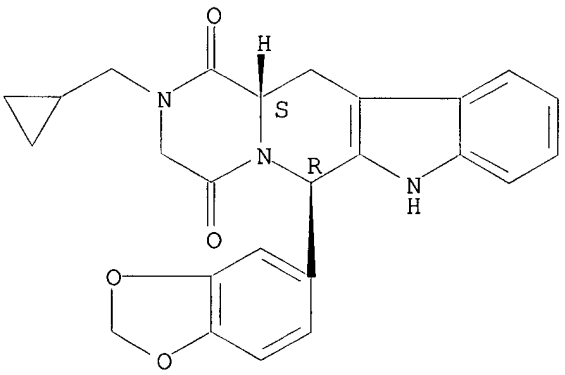
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-butyl-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



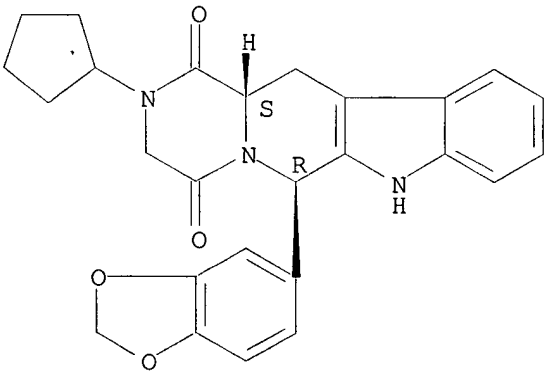
RN 171488-18-9 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-(cyclopropylmethyl)-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



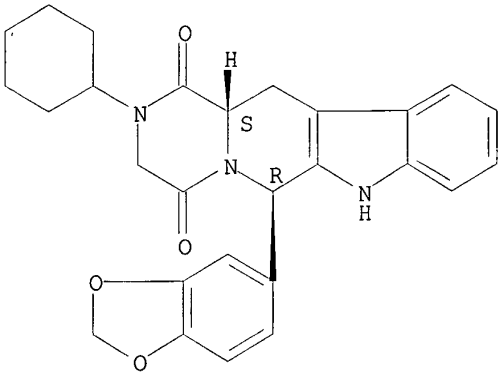
RN 171488-19-0 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclopentyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



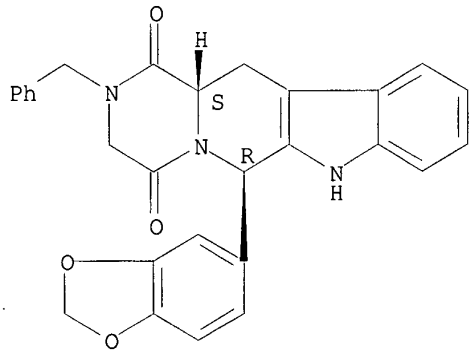
RN 171488-20-3 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclohexyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



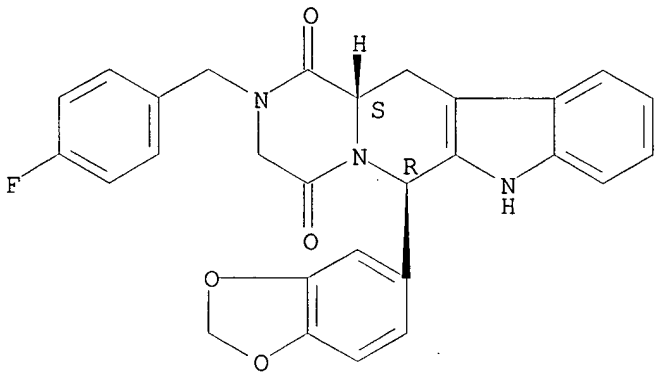
RN 171488-21-4 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(phenylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



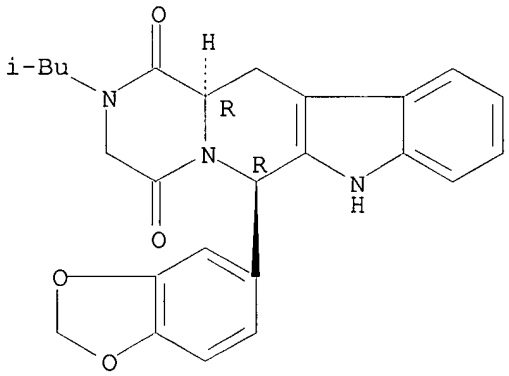
RN 171488-22-5 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[(4-fluorophenyl)methyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



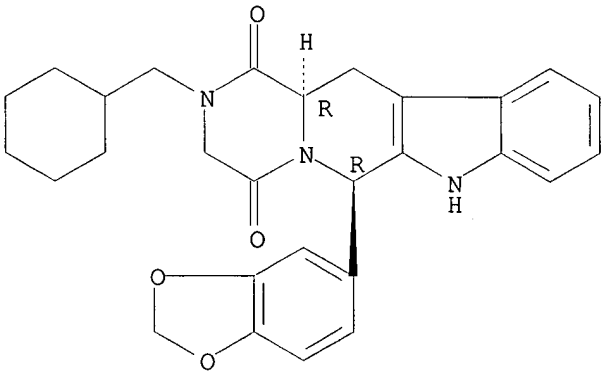
RN 171488-76-9 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-methylpropyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 171488-77-0 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-(cyclohexylmethyl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

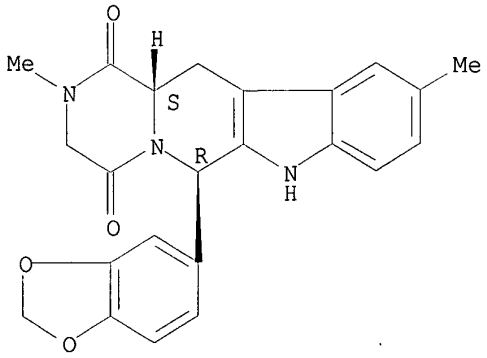
Absolute stereochemistry. Rotation (+).



RN 171488-86-1 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2,10-dimethyl-, (6R,12aS)-rel- (9CI) (CA INDEX

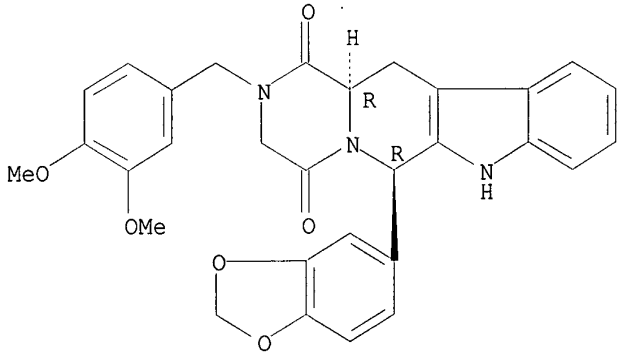
NAME)

Relative stereochemistry.



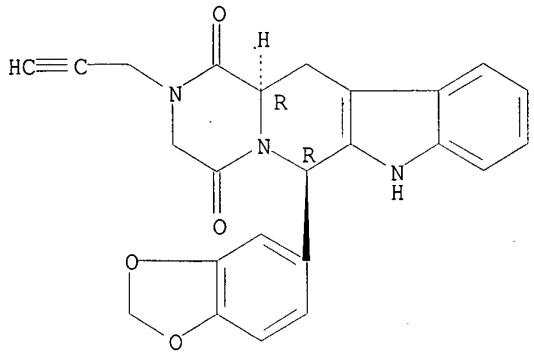
RN 171488-87-2 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[(3,4-dimethoxyphenyl)methyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



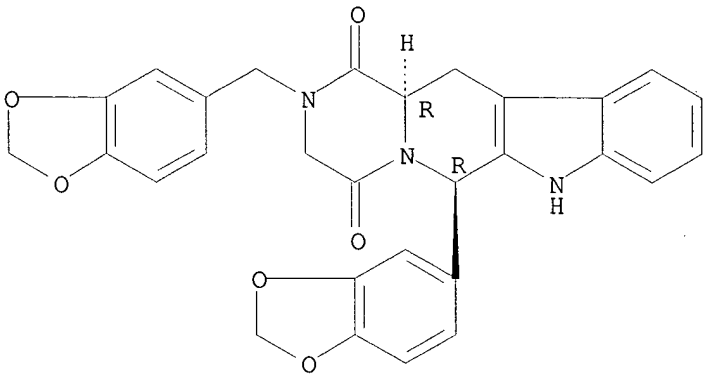
RN 171488-91-8 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-propynyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



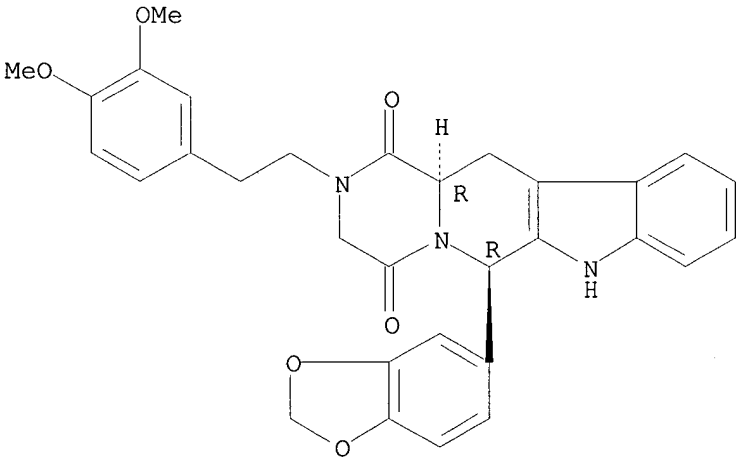
RN 171488-92-9 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-(1,3-benzodioxol-5-ylmethyl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



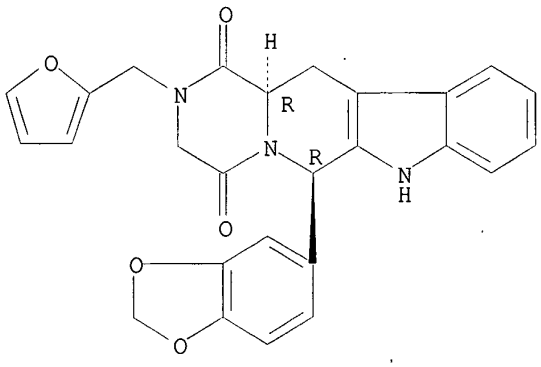
RN 171488-93-0 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[2-(3,4-dimethoxyphenyl)ethyl]-2,3,6,7,12,12a-hexahydro-, (6R-trans)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



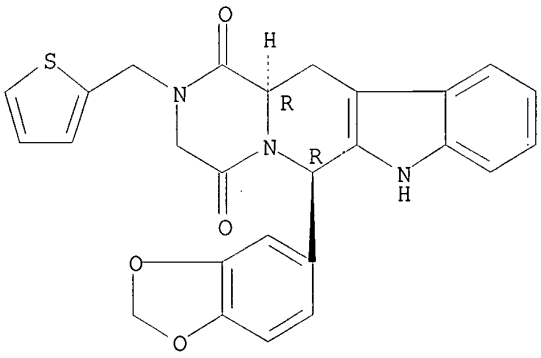
RN 171488-94-1 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-(2-furanylmethyl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



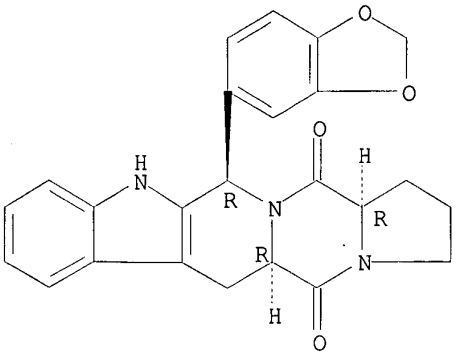
RN 171488-95-2 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-thienylmethyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 171489-01-3 USPATFULL
CN 5H,14H-Pyrrolo[1'',2'':4',5']pyrazino[1',2':1,6]pyrido[3,4-b]indole-5,14-dione, 12-(1,3-benzodioxol-5-yl)-1,2,3,5a,6,11,12,14a-octahydro-, (5aR,12R,14aR)- (9CI) (CA INDEX NAME)

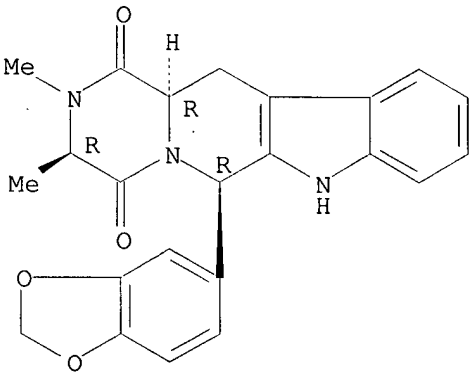
Absolute stereochemistry. Rotation (+).



RN 171489-02-4 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-, (3R,6R,12aR)- (9CI) (CA INDEX

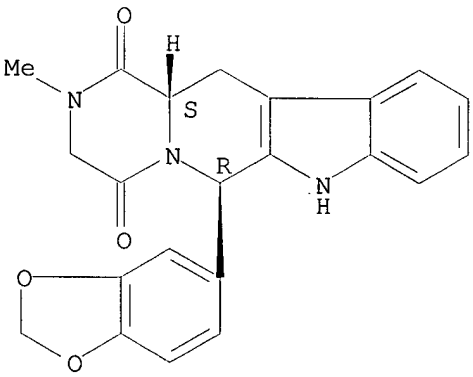
NAME)

Absolute stereochemistry. Rotation (+).



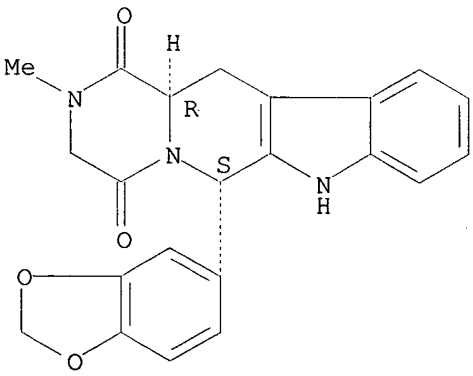
RN 171596-27-3 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 171596-28-4 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6S,12aR)- (9CI) (CA INDEX NAME)

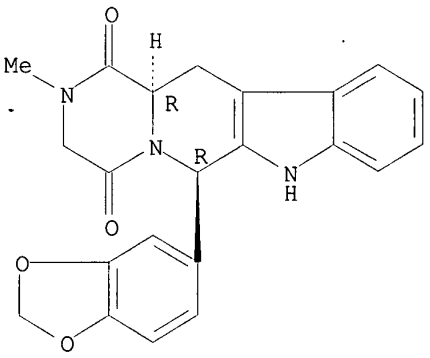
Absolute stereochemistry. Rotation (+).



RN 171596-29-5 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-

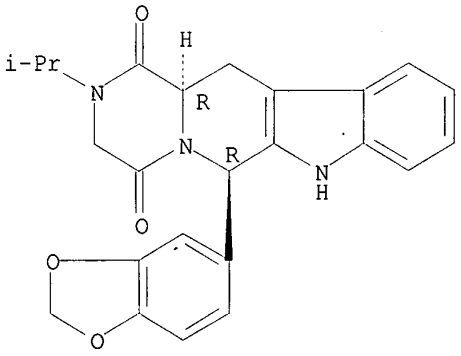
2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



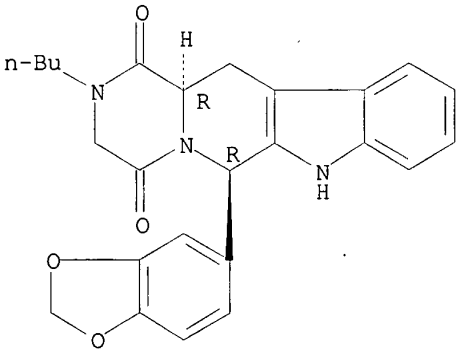
RN 171596-30-8 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(1-methylethyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 171596-31-9 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-butyl-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

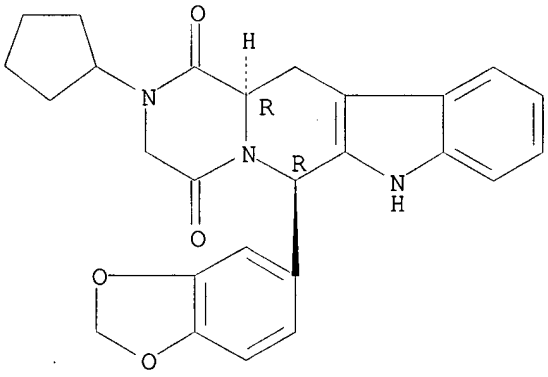
Absolute stereochemistry. Rotation (+).



RN 171596-32-0 USPATFULL

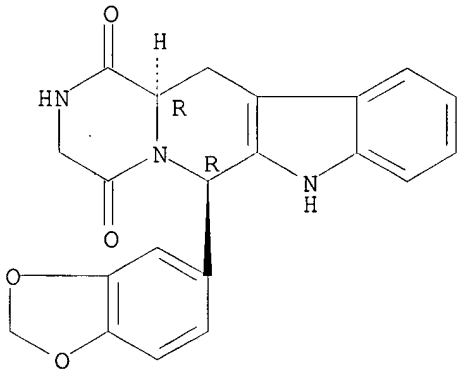
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclopentyl-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



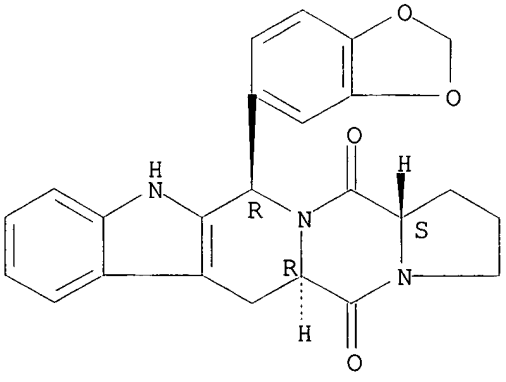
RN 171596-36-4 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



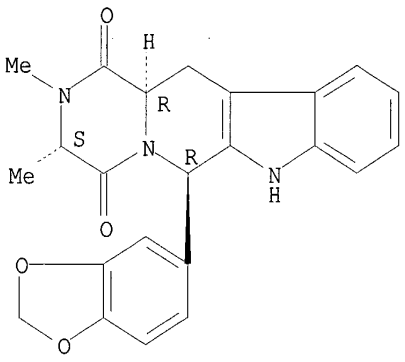
RN 171596-39-7 USPATFULL
CN 5H,14H-Pyrrolo[1'',2'':4',5']pyrazino[1',2':1,6]pyrido[3,4-b]indole-5,14-dione, 12-(1,3-benzodioxol-5-yl)-1,2,3,5a,6,11,12,14a-octahydro-, (5aR,12R,14aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 171596-40-0 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L46 ANSWER 27 OF 63 USPATFULL
ACCESSION NUMBER: 2002:32583 USPATFULL
TITLE: Nitrosated and nitrosylated phosphodiesterase inhibitors, compositions and methods of use
INVENTOR(S): Garvey, David S., Dover, MA, UNITED STATES
Tejada, Inigo Saenz de, Pozuelo de Alarcon, SPAIN
Earl, Richard A., Westford, MA, UNITED STATES
Khanapure, Subhash P., Clinton, MA, UNITED STATES

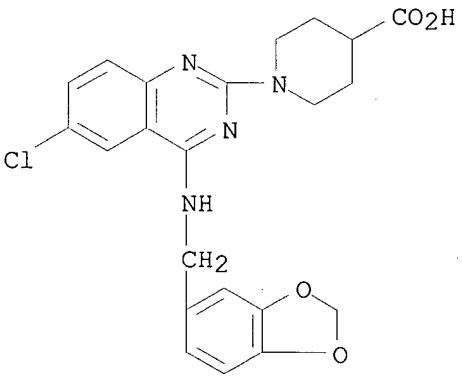
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002019405	A1	20020214
	US 6462044	B2	20021008
APPLICATION INFO.:	US 2001-941691	A1	20010830 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-387727, filed on 1 Sep 1999, PENDING Continuation-in-part of Ser. No. US 1998-145142, filed on 1 Sep 1998, GRANTED, Pat. No. US 5958926 Continuation-in-part of Ser. No. US 1996-740764, filed on 1 Nov 1996, GRANTED, Pat. No. US 5874437 Continuation-in-part of Ser. No. WO 1997-US19870, filed on 31 Oct 1997, UNKNOWN
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: EDWARD D GRIEFF, HALE & DORR LLP, 1455 PENNSYLVANIA AVE, NW, WASHINGTON, DC, 20004
NUMBER OF CLAIMS: 71
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 60 Drawing Page(s)
LINE COUNT: 4113
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention describes novel nitrosated and/or nitrosylated phosphodiesterase inhibitors, and novel compositions containing at least one nitrosated and/or nitrosylated phosphodiesterase inhibitor, and, optionally, one or more compounds that donate, transfer or release nitric oxide, elevate endogenous levels of endothelium-derived relaxing factor, stimulate endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase and/or one or more vasoactive agents. The present invention also provides novel compositions containing at least one phosphodiesterase inhibitor, and one or more compounds that donate,

transfer or release nitric oxide, elevate endogenous levels of endothelium-derived relaxing factor, stimulate endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase and/or one or more vasoactive agents. The present invention also provides methods for treating or preventing sexual dysfunctions in males and females, for enhancing sexual responses in males and females, and for treating or preventing diseases induced by the increased metabolism of cyclic guanosine 3',5'-monophosphate (cGMP), such as **hypertension**, **pulmonary hypertension**, congestive heart failure, renal failure, myocardial infraction, stable, unstable and variant (Prinzmetal) angina, atherosclerosis, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, stroke, asthma, bronchitis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, dementia, immunodeficiency, premature labor, dysmenorrhoea, benign prostatic hyperplasis (BPH), bladder outlet obstruction, incontinence, conditions of reduced blood vessel patency, e.g., postpercutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, allergic rhinitis, glucoma, and diseases characterized by disorders of gut motility, e.g., irritable bowel syndrome (IBS).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **150452-18-9P**, 1-[4-[[(1,3-Benzodioxol-5-yl)methyl]amino]-6-chloro-2-quinazolinyl]-4-piperidinecarboxylic acid
(intermediate; prepn. and uses of nitrosated and nitrosylated phosphodiesterase inhibitors)
RN 150452-18-9 USPATFULL
CN 4-Piperidinecarboxylic acid, 1-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-6-chloro-2-quinazolinyl]- (9CI) (CA INDEX NAME)



L46 ANSWER 28 OF 63 USPATFULL
ACCESSION NUMBER: 2000:150166 USPATFULL
TITLE: Tetracyclic cyclic GMP-specific phosphodiesterase inhibitors, process of preparation and use
INVENTOR(S): Daugan, Alain Claude-Marie, Marly le Roi Cedex, France
Gellibert, Francoise, Marly le Roi Cedex, France
PATENT ASSIGNEE(S): ICOS Corporation, Bothell, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6143746		20001107
APPLICATION INFO.:	US 1998-154051		19980916 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. WO 1995-EP183, filed on 19 Jan 1995, now patented, Pat. No. WO 5859006 which is a continuation-in-part of Ser. No. WO 1996-EP3025,

filed on 11 Jul 1996, now patented, Pat. No. WO 5981527 which is a continuation-in-part of Ser. No. WO 1996-EP3024, filed on 11 Jul 1996

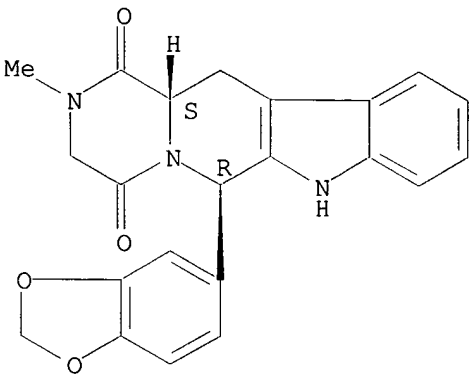
	NUMBER	DATE
PRIORITY INFORMATION:	GB 1994-1090	19940121
	GB 1995-14465	19950714
	GB 1995-14474	19950714

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Cintins, Marianne M.
ASSISTANT EXAMINER: Delacroix-Muirheid, C.
LEGAL REPRESENTATIVE: Marshall, O'Toole, Gerstein, Murray & Borun
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
LINE COUNT: 3174
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A compound of formula (I) and salts and solvates thereof, in which: R.sup.0 represents hydrogen, halogen, or C.sub.1-6 alkyl; R.sup.1 represents hydrogen, C.sub.1-6 alkyl, C.sub.2-6 alkenyl, C.sub.2-6 alkynyl, haloC.sub.1-6 alkyl, C.sub.3-8 cycloalkyl, C.sub.3-8 cycloalkylC.sub.1-3 alkyl, arylC.sub.1-3 alkyl, or heteroarylC.sub.1-3 alkyl; R.sup.2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan, and pyridine, or an optionally substituted bicyclic ring (a) attached to the rest of the molecule via one of the benzene ring carbon atoms, and wherein the fused ring (A) is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated, and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur, and nitrogen; and R.sup.3 represents hydrogen or C.sub.1-3 alkyl, or R.sup.1 and R.sup.3 together represent a 3- or 4-membered alkyl or alkenyl chain. A compound of formula (I) is a potent and selective inhibitor of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP specific PDE) having a utility in a variety of therapeutic areas where such inhibition is beneficial, including the treatment of cardiovascular disorders and erectile dysfunction.

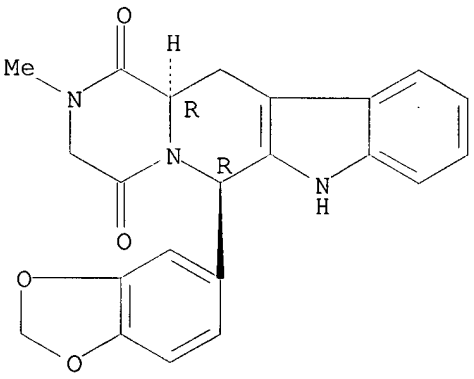
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **171488-01-0P 171488-03-2P 171488-04-3P**
171488-06-5P 171488-07-6P 171488-08-7P
171488-09-8P 171488-10-1P 171488-11-2P
171488-12-3P 171488-13-4P 171488-14-5P
171488-15-6P 171488-16-7P 171488-17-8P
171488-18-9P 171488-19-0P 171488-20-3P
171488-21-4P 171488-22-5P 171488-76-9P
171488-77-0P 171488-86-1P 171488-87-2P
171488-91-8P 171488-92-9P 171488-94-1P
171488-95-2P 171489-01-3P 171489-02-4P
171596-27-3P 171596-28-4P 171596-29-5P
171596-30-8P 171596-31-9P 171596-32-0P
171596-36-4P 171596-39-7P 171596-40-0P
187935-15-5P 303984-32-9P
(tetracyclic cyclic GMP-specific phosphodiesterase inhibitors and their use in disease treatment)
RN 171488-01-0 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



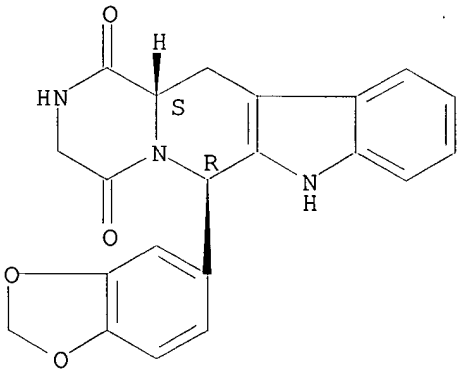
RN 171488-03-2 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



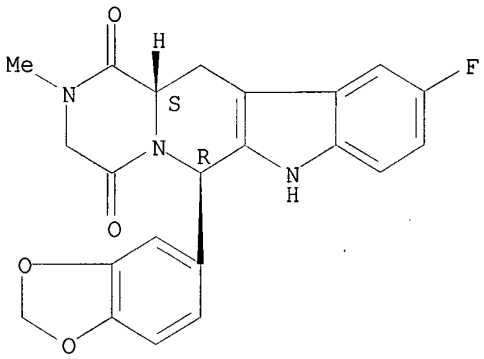
RN 171488-04-3 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



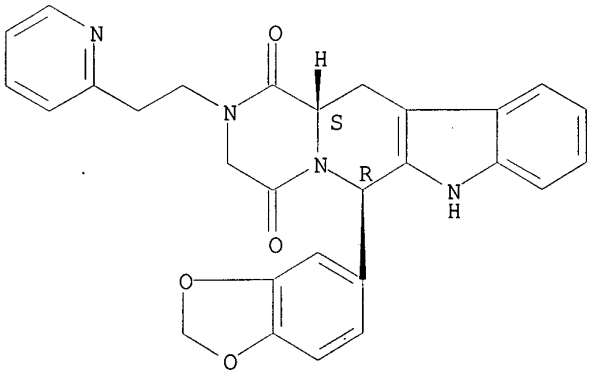
RN 171488-06-5 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-10-fluoro-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



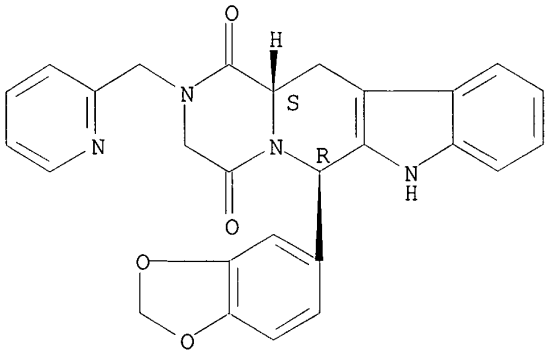
RN 171488-07-6 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[2-(2-pyridinyl)ethyl]-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



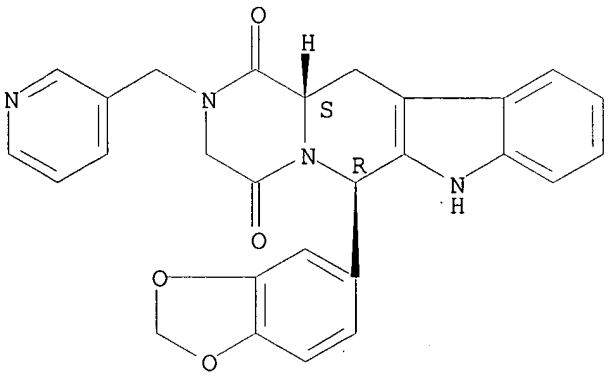
RN 171488-08-7 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-pyridinylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



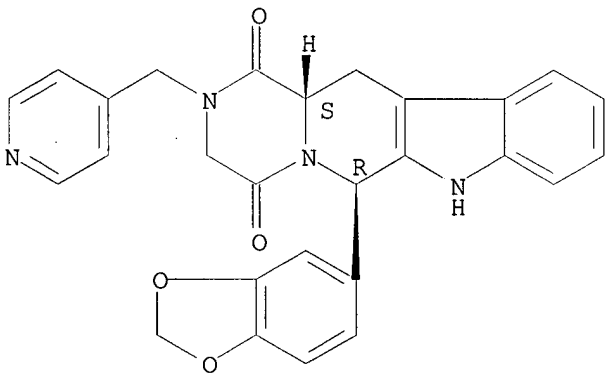
RN 171488-09-8 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(3-pyridinylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



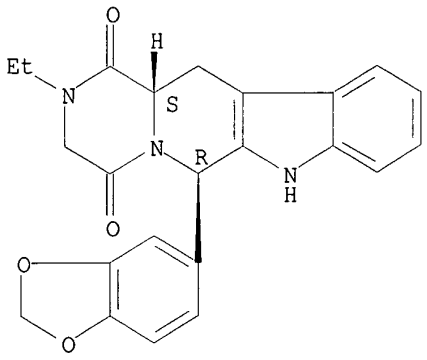
RN 171488-10-1 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(4-pyridinylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



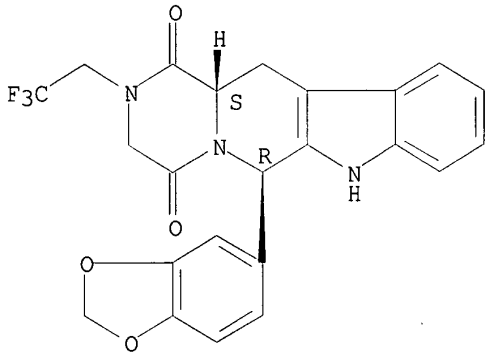
RN 171488-11-2 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-ethyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



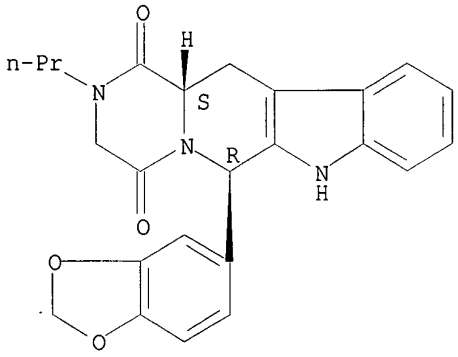
RN 171488-12-3 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2,2,2-trifluoroethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 171488-13-4 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-propyl-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

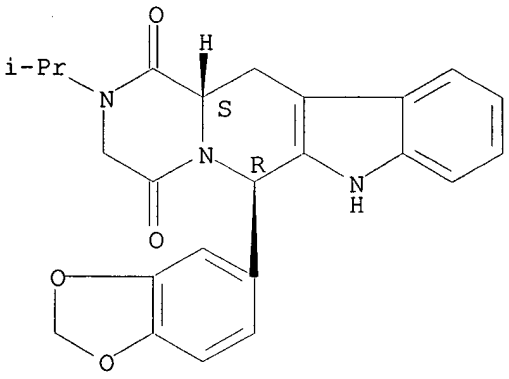
Relative stereochemistry.



RN 171488-14-5 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(1-methylethyl)-, (6R,12aS)-rel- (9CI) (CA

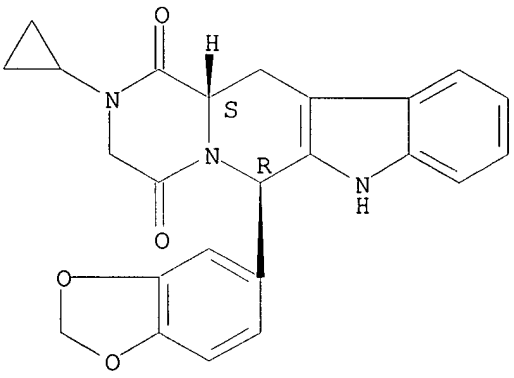
INDEX NAME)

Relative stereochemistry.



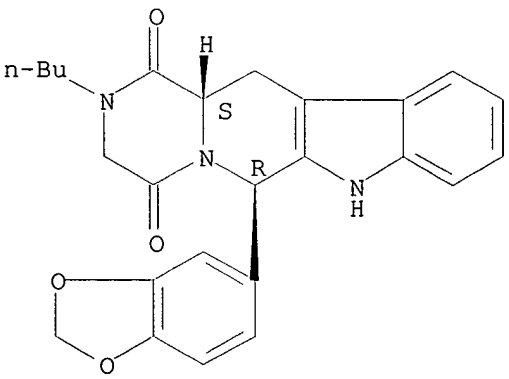
RN 171488-15-6 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclopropyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 171488-16-7 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-butyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

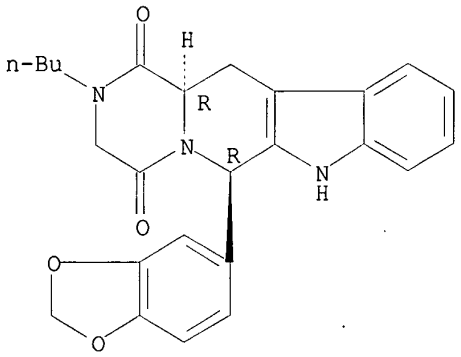
Relative stereochemistry.



RN 171488-17-8 USPATFULL

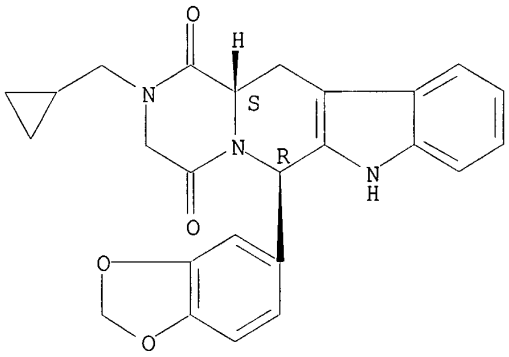
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-butyl-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



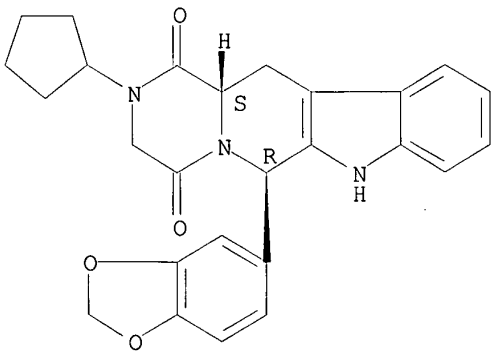
RN 171488-18-9 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-(cyclopropylmethyl)-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



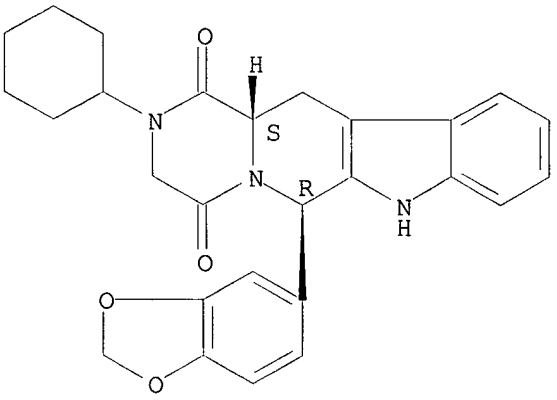
RN 171488-19-0 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclopentyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



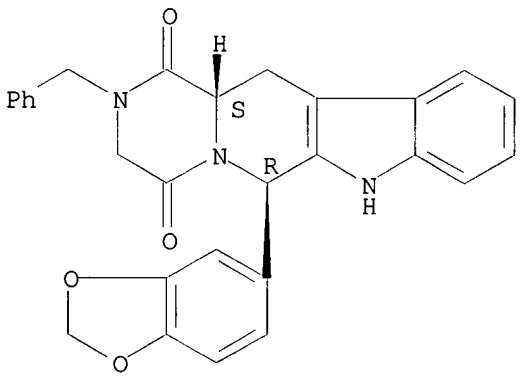
RN 171488-20-3 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclohexyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



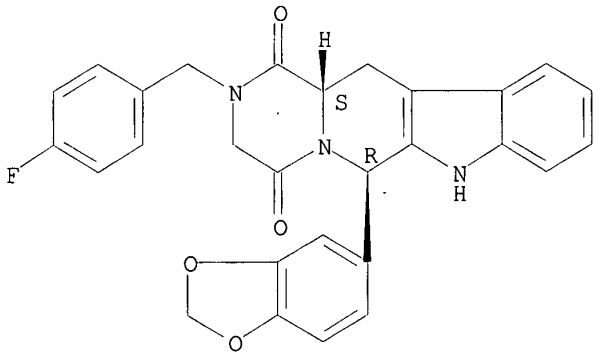
RN 171488-21-4 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(phenylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



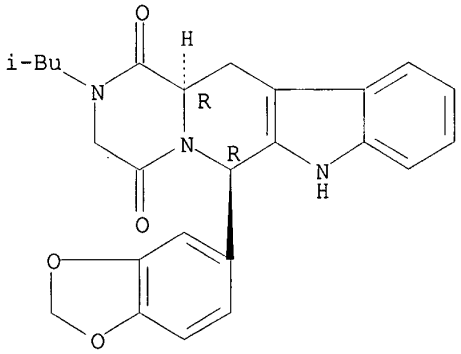
RN 171488-22-5 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[(4-fluorophenyl)methyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



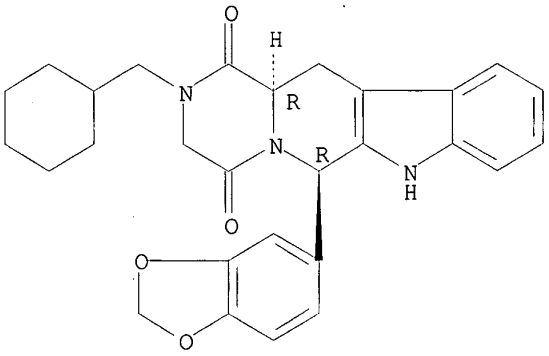
RN 171488-76-9 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-methylpropyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 171488-77-0 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-(cyclohexylmethyl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

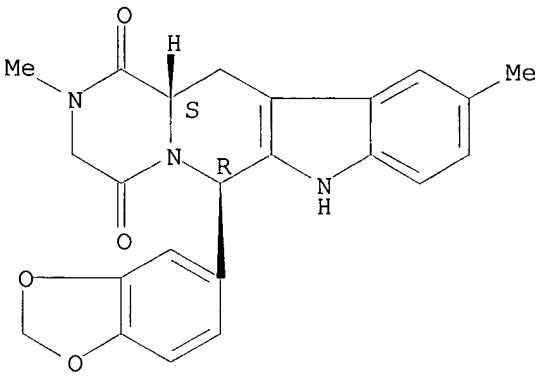
Absolute stereochemistry. Rotation (+).



RN 171488-86-1 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2,10-dimethyl-, (6R,12aS)-rel- (9CI) (CA INDEX

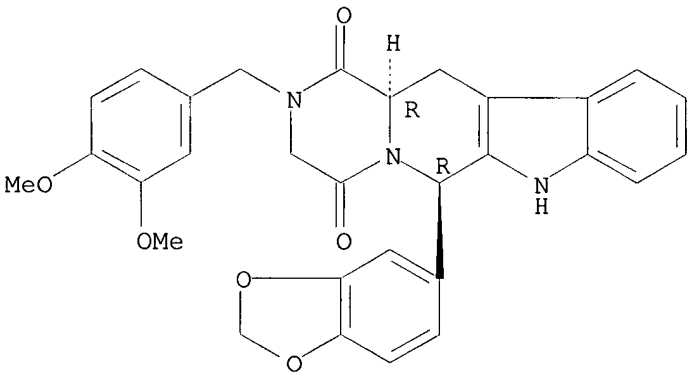
NAME)

Relative stereochemistry.



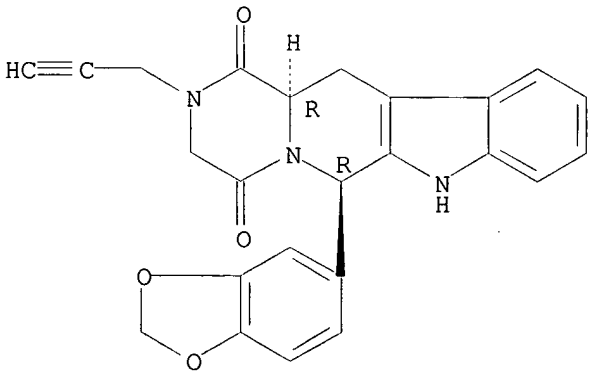
RN 171488-87-2 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[(3,4-dimethoxyphenyl)methyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



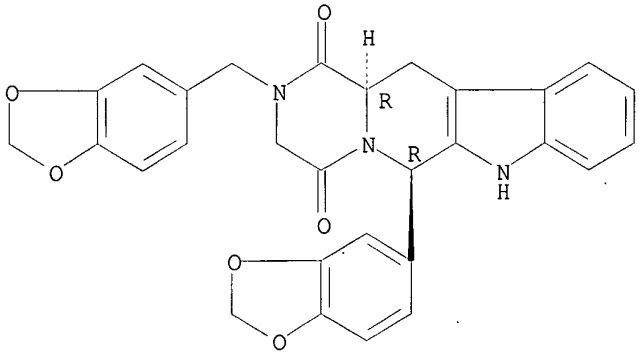
RN 171488-91-8 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-propynyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



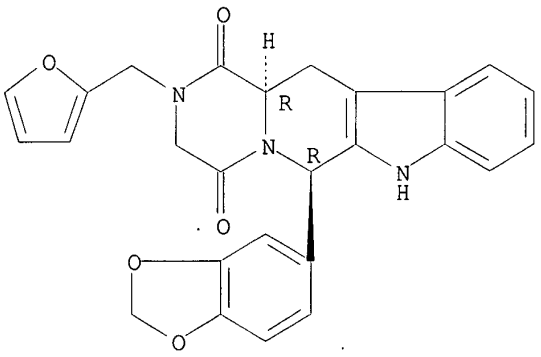
RN 171488-92-9 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-(1,3-benzodioxol-5-ylmethyl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



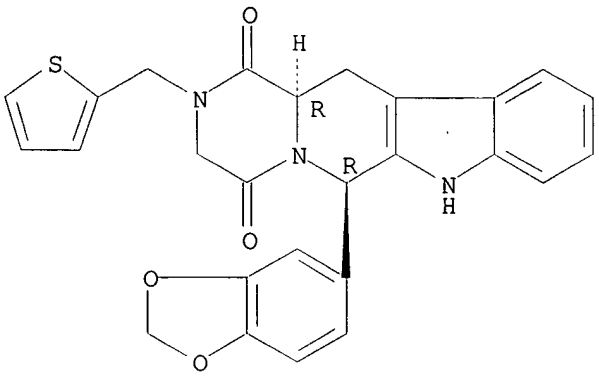
RN 171488-94-1 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-(2-furanylmethyl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



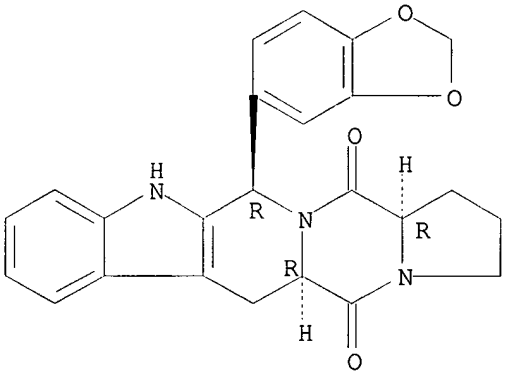
RN 171488-95-2 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-thienylmethyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



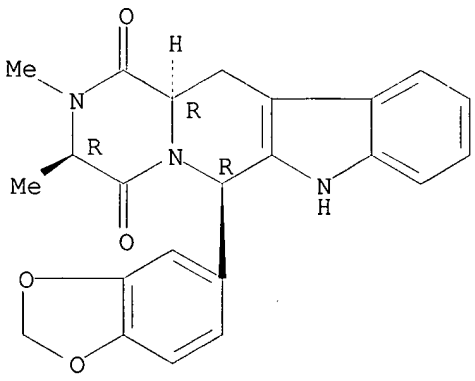
RN 171489-01-3 USPATFULL
CN 5H,14H-Pyrrolo[1'',2'':4',5']pyrazino[1',2':1,6]pyrido[3,4-b]indole-5,14-dione, 12-(1,3-benzodioxol-5-yl)-1,2,3,5a,6,11,12,14a-octahydro-, (5aR,12R,14aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



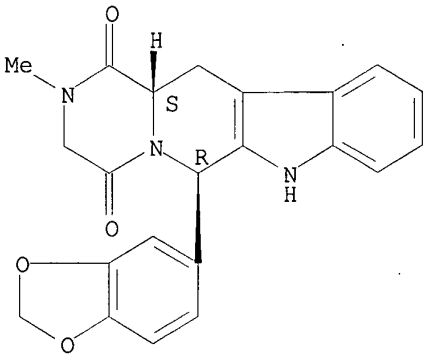
RN 171489-02-4 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-, (3R,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



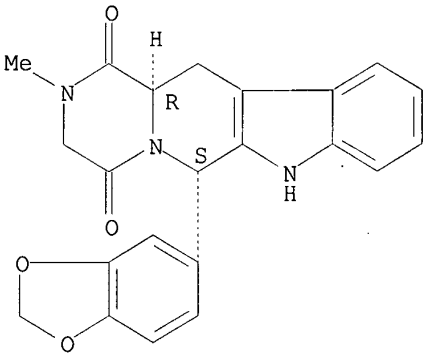
RN 171596-27-3 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



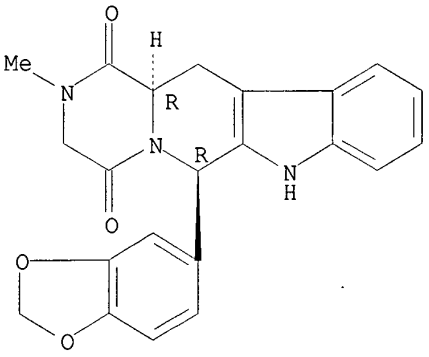
RN 171596-28-4 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6S,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 171596-29-5 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

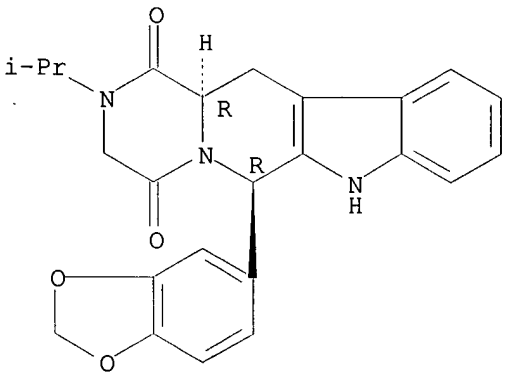
Absolute stereochemistry. Rotation (+).



RN 171596-30-8 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(1-methylethyl)-, (6R,12aR)- (9CI) (CA INDEX

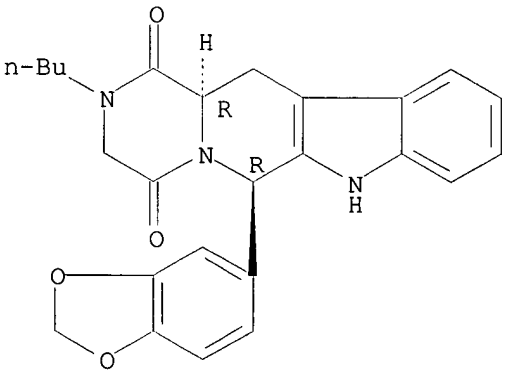
NAME)

Absolute stereochemistry. Rotation (+).



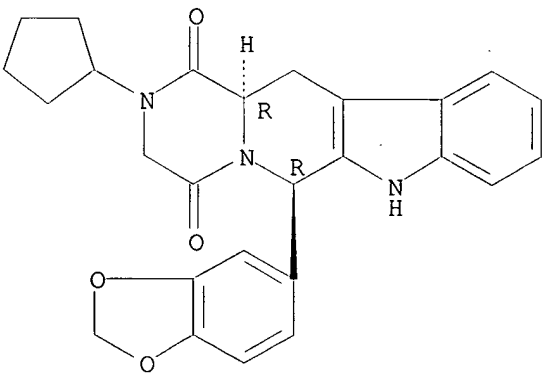
RN 171596-31-9 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-butyl-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 171596-32-0 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclopentyl-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

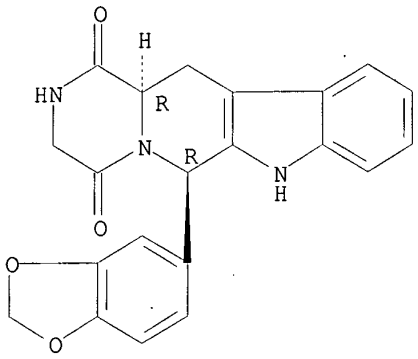
Absolute stereochemistry. Rotation (+).



RN 171596-36-4 USPATFULL

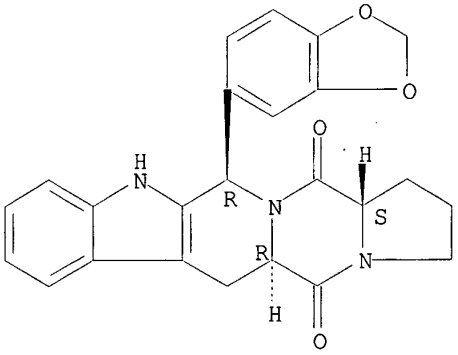
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



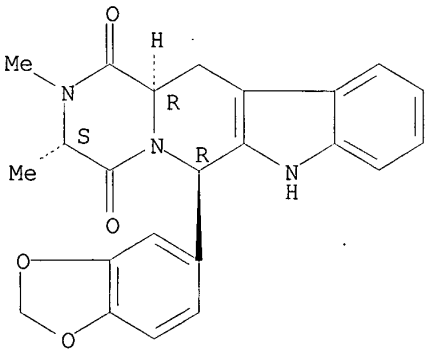
RN 171596-39-7 USPATFULL
CN 5H,14H-Pyrrolo[1'',2'':4',5']pyrazino[1',2':1,6]pyrido[3,4-b]indole-5,14-dione, 12-(1,3-benzodioxol-5-yl)-1,2,3,5a,6,11,12,14a-octahydro-, (5aR,12R,14aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



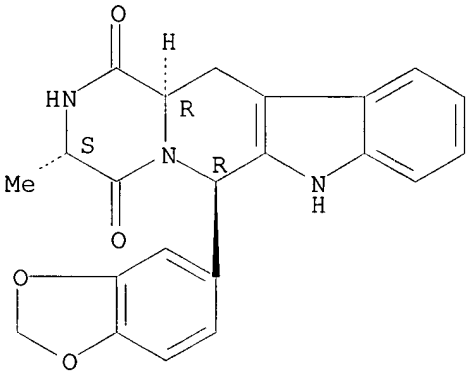
RN 171596-40-0 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



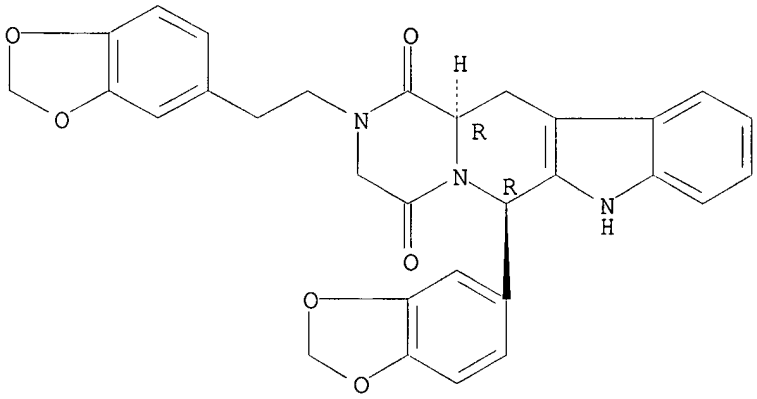
RN 187935-15-5 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-3-methyl-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 303984-32-9 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[2-(1,3-benzodioxol-5-yl)ethyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L46 ANSWER 29 OF 63 USPATFULL

ACCESSION NUMBER:	1999:4663 USPATFULL			
TITLE:	Tetracyclic derivatives; process of preparation and use			
INVENTOR(S):	Daugan, Alain Claude-Marie, Les Ulis, France			
PATENT ASSIGNEE(S):	ICOS Corporation, Bothell, WA, United States (U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5859006		19990112	
	WO 9519978		19950727	
APPLICATION INFO.:	US 1996-669389		19960716	(8)
	WO 1995-EP183		19950119	
			19960717	PCT 371 date
			19960717	PCT 102(e) date

NUMBER DATE

Searched by Barb O'Bryen, STIC 308-4291

PRIORITY INFORMATION:	GB 1994-1090	19940121
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	Granted	
PRIMARY EXAMINER:	Shah, Mukund J.	
ASSISTANT EXAMINER:	Ngo, Tamthom T.	
LEGAL REPRESENTATIVE:	Marshall, O'Toole, Gerstein, Murray & Borun	
NUMBER OF CLAIMS:	15	
EXEMPLARY CLAIM:	1	
LINE COUNT:	2580	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A compound of formula (I) ##STR1## and salts and solvates thereof, in which: R.sup.0 represents hydrogen, halogen or C.sub.1-6 alkyl;

R.sup.1 represents hydrogen, C.sub.1-6 alkyl, C.sub.2-6 alkenyl, C.sub.2-6 alkynyl, haloC.sub.1-6 alkyl, C.sub.3-8 cycloalkyl, C.sub.3-8 cycloalkylC.sub.1-3 alkyl, arylC.sub.1-3 alkyl or heteroarylC.sub.1-3 alkyl; R.sup.2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring ##STR2## attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen; and

R.sup.3 represents hydrogen or C.sub.1-3 alkyl, or R.sup.1 and R.sup.3 together represent a 3- or 4-membered alkyl or alkenyl chain.

A compound of formula (I) is a potent and selective inhibitor of cyclic guanosine 3', 5'-monophosphate specific phosphodiesterase (cGMP specific PDE) having a utility in a variety of therapeutic areas where such inhibition is beneficial, including the treatment of cardiovascular disorders.

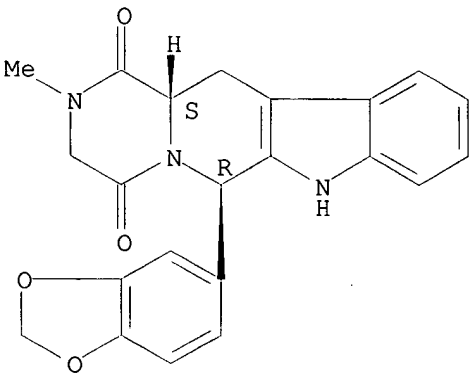
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **171488-01-0P 171488-03-2P 171488-04-3P**
171488-06-5P 171488-07-6P 171488-08-7P
171488-09-8P 171488-10-1P 171488-11-2P
171488-12-3P 171488-13-4P 171488-14-5P
171488-15-6P 171488-16-7P 171488-17-8P
171488-18-9P 171488-19-0P 171488-20-3P
171488-21-4P 171488-22-5P 171488-76-9P
171488-77-0P 171488-86-1P 171488-87-2P
171488-91-8P 171488-92-9P 171488-93-0P
171488-94-1P 171488-95-2P 171489-01-3P
171489-02-4P 171596-27-3P 171596-28-4P
171596-29-5P 171596-30-8P 171596-31-9P
171596-32-0P 171596-36-4P 171596-39-7P
171596-40-0P
(prepn. of pyrazinopyridoindolediones as inhibitors of cyclic guanosine monophosphate specific phosphodiesterase)

RN 171488-01-0 USPATFULL

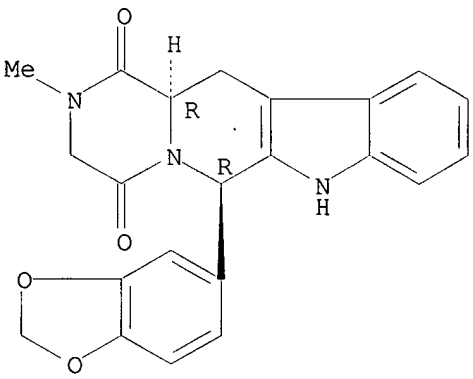
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



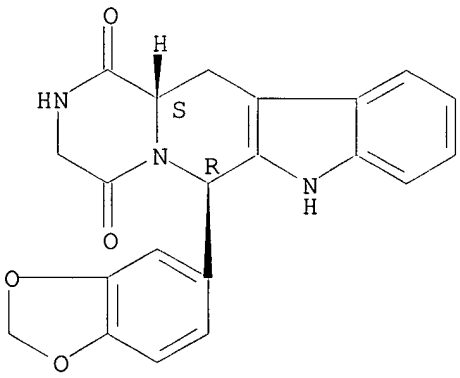
RN 171488-03-2 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



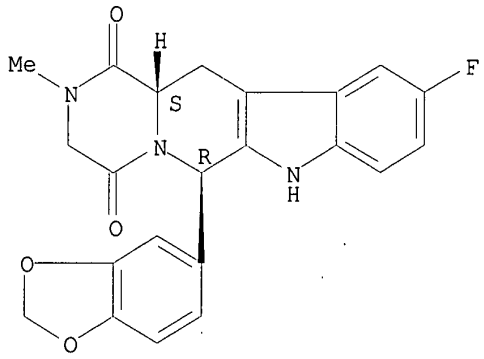
RN 171488-04-3 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



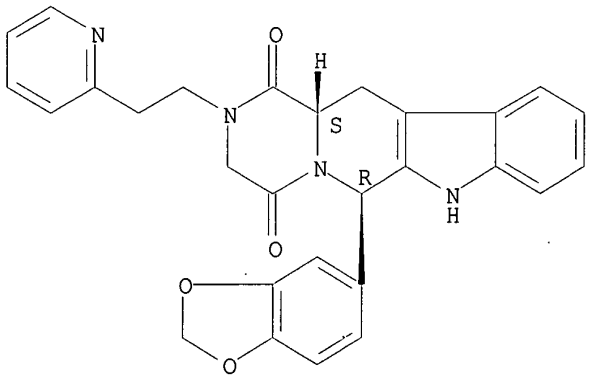
RN 171488-06-5 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-10-fluoro-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



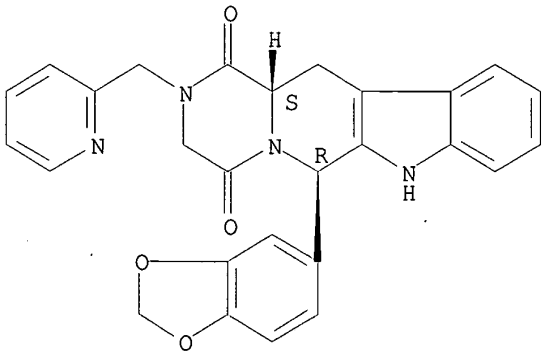
RN 171488-07-6 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-[2-(2-pyridinyl)ethyl]-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



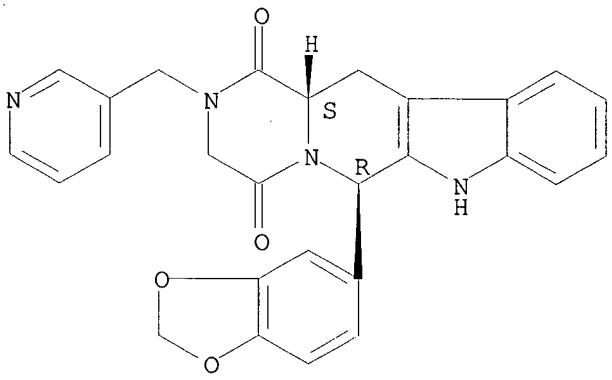
RN 171488-08-7 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-pyridinylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



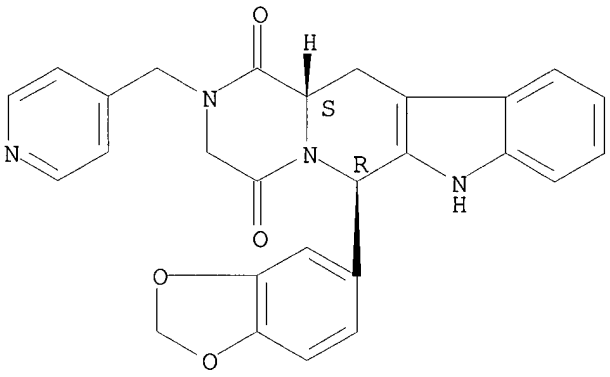
RN 171488-09-8 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(3-pyridinylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



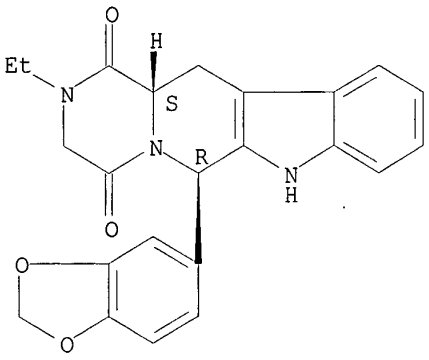
RN 171488-10-1 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(4-pyridinylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



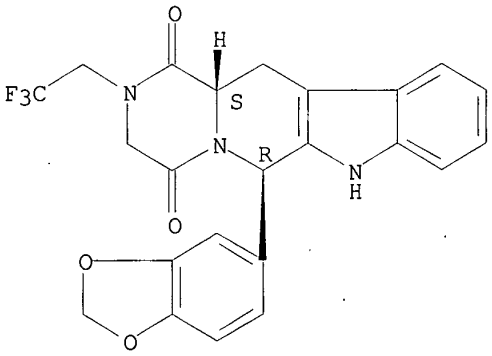
RN 171488-11-2 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-ethyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



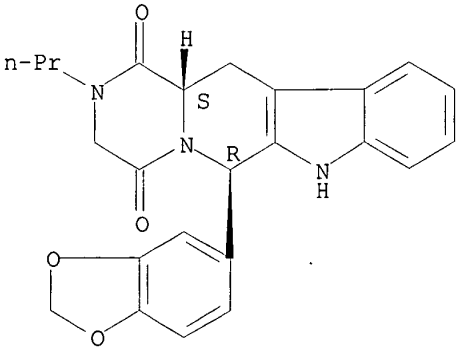
RN 171488-12-3 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2,2,2-trifluoroethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 171488-13-4 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-propyl-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

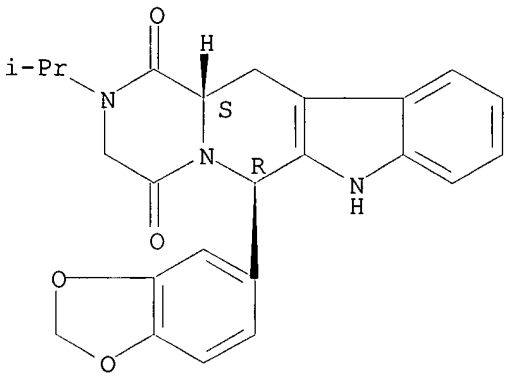
Relative stereochemistry.



RN 171488-14-5 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(1-methylethyl)-, (6R,12aS)-rel- (9CI) (CA

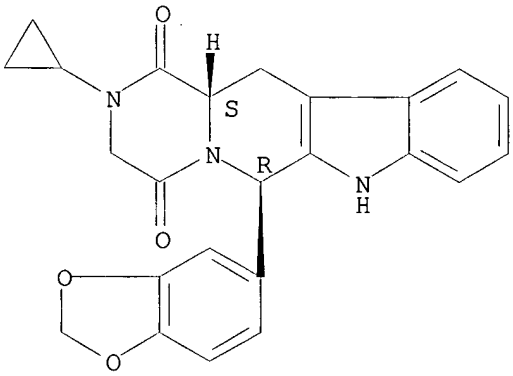
INDEX NAME)

Relative stereochemistry.



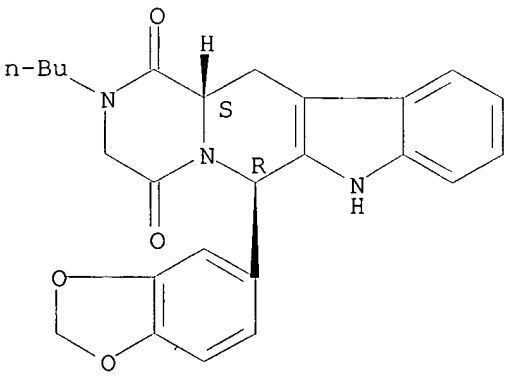
RN 171488-15-6 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclopropyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 171488-16-7 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-butyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

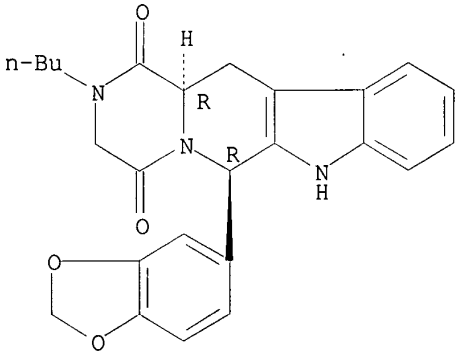
Relative stereochemistry.



RN 171488-17-8 USPATFULL

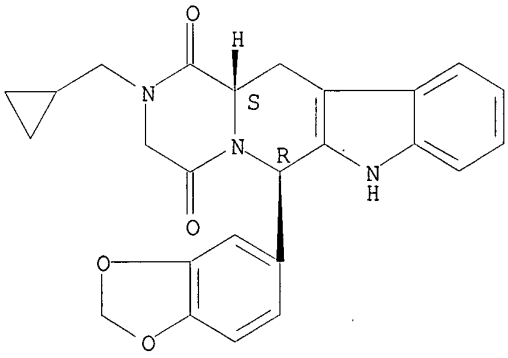
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-butyl-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



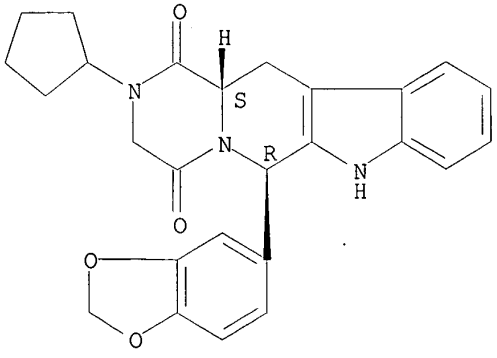
RN 171488-18-9 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-(cyclopropylmethyl)-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



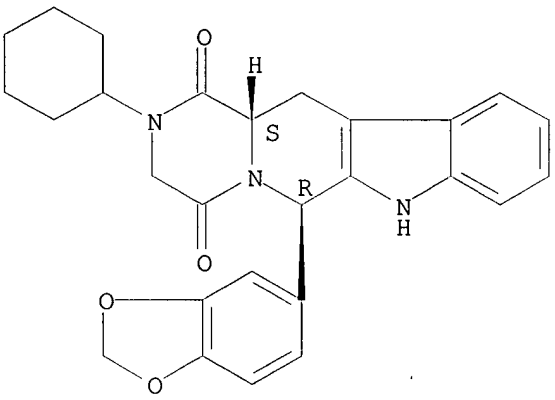
RN 171488-19-0 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclopentyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



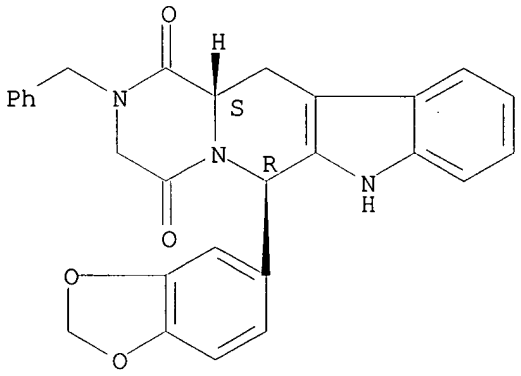
RN 171488-20-3 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclohexyl-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



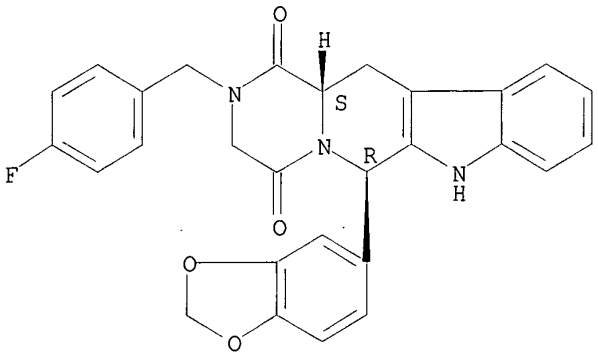
RN 171488-21-4 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(phenylmethyl)-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



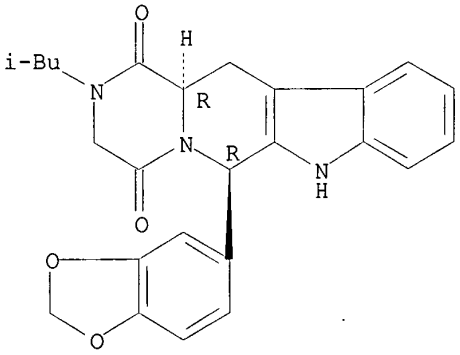
RN 171488-22-5 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[(4-fluorophenyl)methyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aS)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



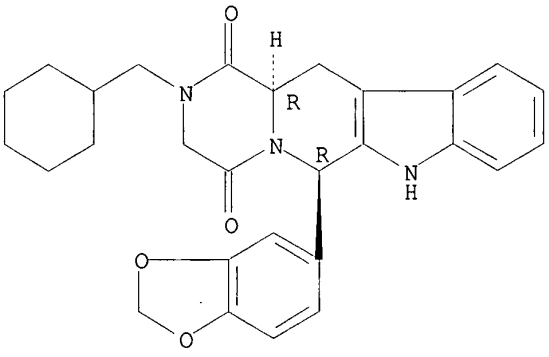
RN 171488-76-9 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-methylpropyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 171488-77-0 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-(cyclohexylmethyl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

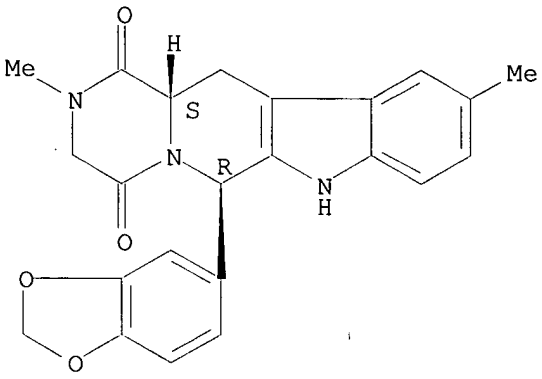
Absolute stereochemistry. Rotation (+).



RN 171488-86-1 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2,10-dimethyl-, (6R,12aS)-rel- (9CI) (CA INDEX

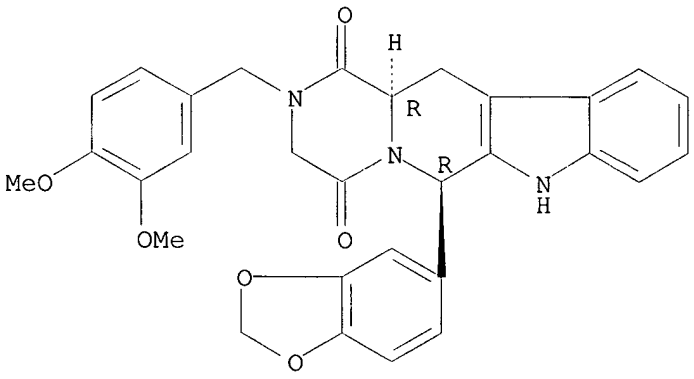
NAME)

Relative stereochemistry.



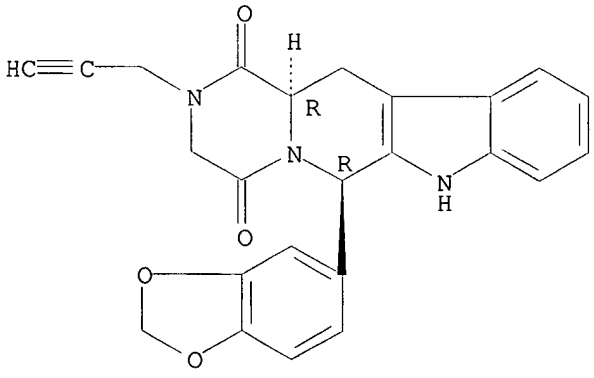
RN 171488-87-2 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[(3,4-dimethoxyphenyl)methyl]-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



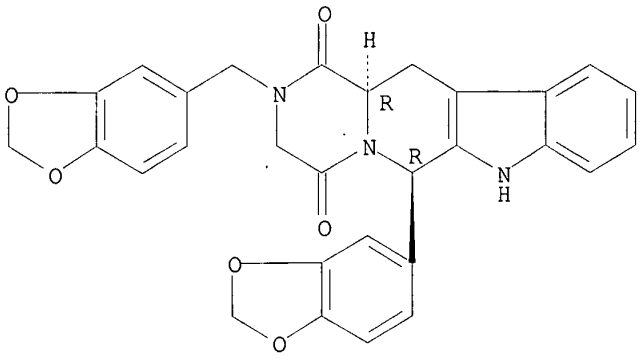
RN 171488-91-8 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-propynyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



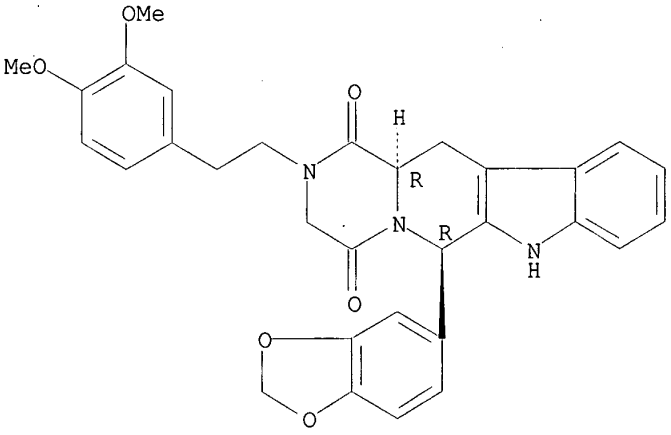
RN 171488-92-9 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-(1,3-benzodioxol-5-ylmethyl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



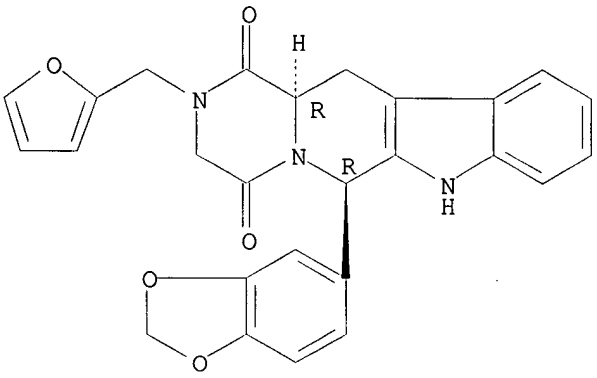
RN 171488-93-0 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-[2-(3,4-dimethoxyphenyl)ethyl]-2,3,6,7,12,12a-hexahydro-, (6R-trans)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



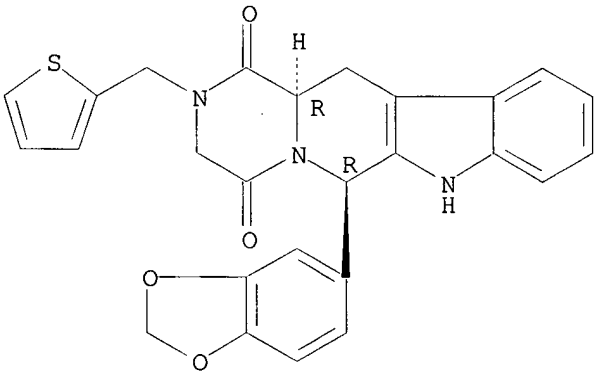
RN 171488-94-1 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-(2-furanylmethyl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



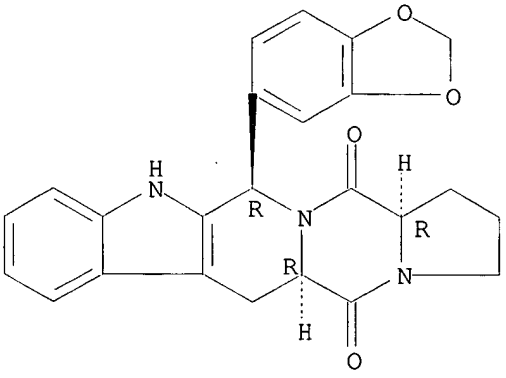
RN 171488-95-2 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(2-thienylmethyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 171489-01-3 USPATFULL
CN 5H,14H-Pyrrolo[1'',2'':4',5']pyrazino[1',2':1,6]pyrido[3,4-b]indole-5,14-dione, 12-(1,3-benzodioxol-5-yl)-1,2,3,5a,6,11,12,14a-octahydro-, (5aR,12R,14aR)- (9CI) (CA INDEX NAME)

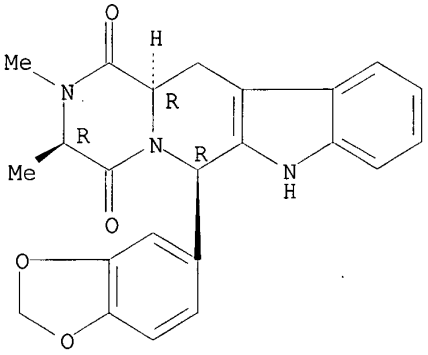
Absolute stereochemistry. Rotation (+).



RN 171489-02-4 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-, (3R,6R,12aR)- (9CI) (CA INDEX

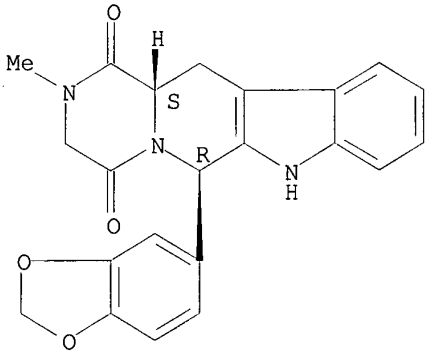
NAME)

Absolute stereochemistry. Rotation (+).



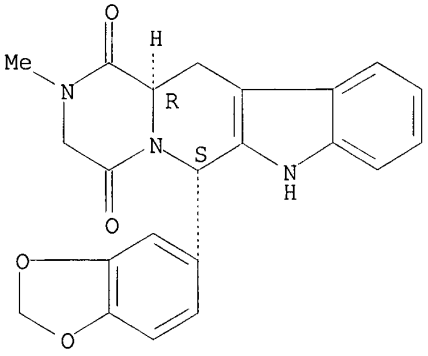
RN 171596-27-3 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 171596-28-4 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6S,12aR)- (9CI) (CA INDEX NAME)

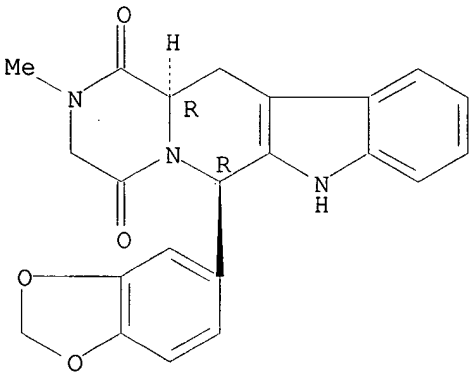
Absolute stereochemistry. Rotation (+).



RN 171596-29-5 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-

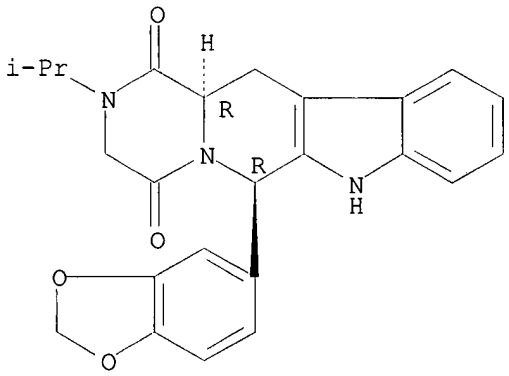
2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



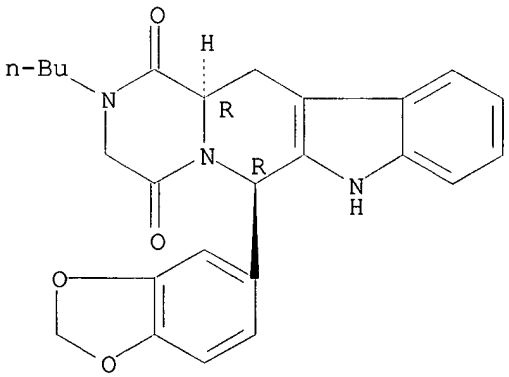
RN 171596-30-8 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-(1-methylethyl)-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 171596-31-9 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-butyl-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

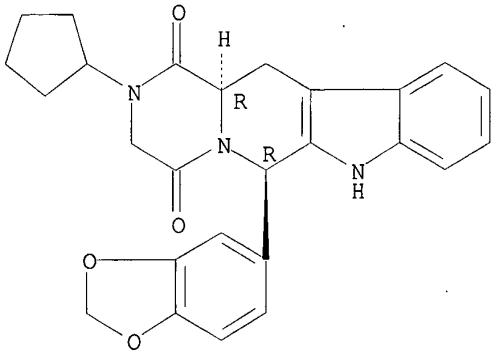
Absolute stereochemistry. Rotation (+).



RN 171596-32-0 USPATFULL

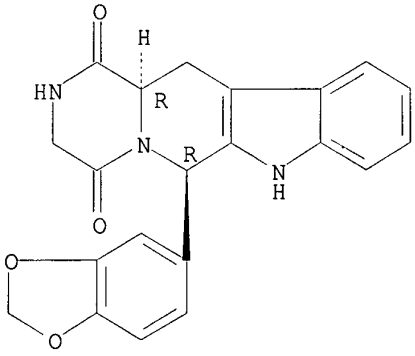
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2-cyclopentyl-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



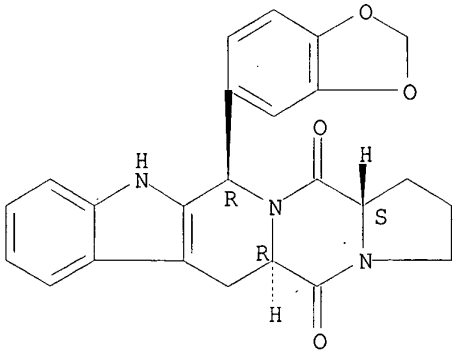
RN 171596-36-4 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-, (6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



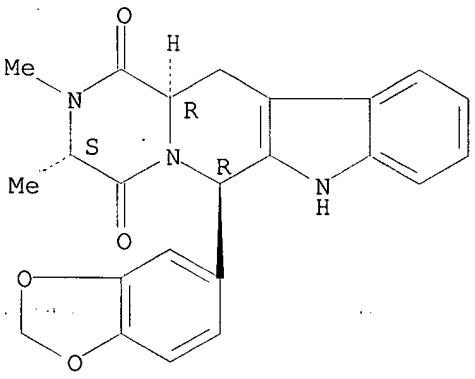
RN 171596-39-7 USPATFULL
CN 5H,14H-Pyrrolo[1'',2'':4',5']pyrazino[1',2':1,6]pyrido[3,4-b]indole-5,14-dione, 12-(1,3-benzodioxol-5-yl)-1,2,3,5a,6,11,12,14a-octahydro-, (5aR,12R,14aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 171596-40-0 USPATFULL
CN Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-, (3S,6R,12aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L46 ANSWER 30 OF 63 MEDLINE
ACCESSION NUMBER: 2003040393 MEDLINE
DOCUMENT NUMBER: 22436084 PubMed ID: 12547578
TITLE: Sildenafil for lung fibrosis and pulmonary hypertension.
COMMENT: Comment on: Lancet. 2002 Sep 21;360(9337):895-900
AUTHOR: Kleinsasser Axel; Loeckinger Alex
SOURCE: LANCET, (2003 Jan 18) 361 (9353) 262-3; author reply 263.
Journal code: 2985213R. ISSN: 0140-6736.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Commentary
Letter
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20030128
Last Updated on STN: 20030206
Entered Medline: 20030205
CONTROLLED TERM: Check Tags: Human
Hypertension, Pulmonary: CO, complications
***Hypertension, Pulmonary: DT, drug therapy**
*Oxygen: AD, administration & dosage
*Piperazines: TU, therapeutic use
Pulmonary Fibrosis: CO, complications
*Pulmonary Fibrosis: DT, drug therapy
Pulmonary Gas Exchange: DE, drug effects
*Vasodilator Agents: TU, therapeutic use
CAS REGISTRY NO.: 139755-83-2 **(sildenafil)**; 7782-44-7 (Oxygen)
CHEMICAL NAME: 0 (Piperazines); 0 (Vasodilator Agents)

Registry record for Medline hit printed at end

L46 ANSWER 31 OF 63 MEDLINE
ACCESSION NUMBER: 2003030820 MEDLINE
DOCUMENT NUMBER: 22425809 PubMed ID: 12538421
TITLE: Beneficial effects of phosphodiesterase 5 inhibition in pulmonary hypertension are influenced by natriuretic Peptide activity.
AUTHOR: Zhao Lan; Mason Nicola A; Strange Julian W; Walker Hamish;

Wilkins Martin R
CORPORATE SOURCE: Section on Clinical Pharmacology, Imperial College School of Science, Technology and Medicine, Hammersmith Hospital, London, England.
SOURCE: CIRCULATION, (2003 Jan 21) 107 (2) 234-7.
Journal code: 0147763. ISSN: 1524-4539.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20030123
Last Updated on STN: 20030129
Entered Medline: 20030128

ABSTRACT:
BACKGROUND: Phosphodiesterase type 5 (PDE5) inhibitors (eg, sildenafil) are a novel, orally active approach to the treatment of pulmonary arterial hypertension. The role of natriuretic peptides in the response to sildenafil was examined in mice lacking NPR-A, a guanylyl cyclase-linked natriuretic peptide receptor, in which pulmonary hypertension was induced by hypoxia. METHODS AND RESULTS: Mice homozygous for NPR-A (NPR-A+/+) and null mutants (NPR-A-/-) were studied. Sildenafil inhibited the pressor response to acute hypoxia in the isolated perfused lungs of both genotypes. This effect was greater in the presence of atrial natriuretic peptide in the perfusate in NPR-A+/+ mice but not NPR-A-/- animals. In vivo, NPR-A mutants had higher basal right ventricular (RV) systolic pressures (RVSPs) than did NPR-A+/+ mice, and this was not affected by 3 weeks of treatment with sildenafil (25 mg x kg(-1) x d(-1)). Both genotypes exhibited a rise in RVSP and RV weight with chronic hypoxia (10% O2 for 21 days); RVSP and RV weight were reduced by continuous sildenafil administration in NPR-A+/+ mice, but only RVSP showed evidence of a response to the drug in NPR-A-/- mice. The effect of sildenafil on hypoxia-induced pulmonary vascular muscularization and cyclic GMP levels was also blunted in NPR-A-/- mice. CONCLUSIONS: The natriuretic peptide pathway influences the response to PDE5 inhibition in hypoxia-induced pulmonary hypertension, particularly its effects on RV hypertrophy and vascular remodeling.

CONTROLLED TERM: Check Tags: Animal; In Vitro; Support, Non-U.S. Gov't
Anoxia: CO, complications
*Anoxia: PP, physiopathology
*Atrial Natriuretic Factor: ME, metabolism
Blood Pressure: DE, drug effects
Cyclic GMP: ME, metabolism
Disease Models, Animal
*Guanylate Cyclase: DF, deficiency
Guanylate Cyclase: GE, genetics
Homozygote
Hypertension, Pulmonary: DT, drug therapy
Hypertension, Pulmonary: ET, etiology
***Hypertension, Pulmonary: PP, physiopathology**
Hypertrophy, Right Ventricular: ET, etiology
Hypertrophy, Right Ventricular: PC, prevention & control
Lung: BS, blood supply
Lung: DE, drug effects
Lung: PP, physiopathology
Mice
Mice, Mutant Strains
Perfusion
*Phosphodiesterase Inhibitors: PD, pharmacology
Phosphoric Diester Hydrolases: DE, drug effects
*Phosphoric Diester Hydrolases: ME, metabolism
Piperazines: PD, pharmacology
*Receptors, Atrial Natriuretic Factor: DF, deficiency

Receptors, Atrial Natriuretic Factor: GE, genetics
Respiration, Artificial
Ventricular Function, Right: DE, drug effects
CAS REGISTRY NO.: **139755-83-2 (sildenafil)**; 7665-99-8 (Cyclic GMP); 85637-73-6 (Atrial Natriuretic Factor)
CHEMICAL NAME: 0 (Phosphodiesterase Inhibitors); 0 (Piperazines); 0 (Receptors, Atrial Natriuretic Factor); 0 (atrial natriuretic factor receptor A); EC 3.1.4 (Phosphoric Diester Hydrolases); EC 3.1.4.- (phosphodiesterase V); EC 4.6.1.2 (Guanylate Cyclase)

L46 ANSWER 32 OF 63 MEDLINE
ACCESSION NUMBER: 2002408505 MEDLINE
DOCUMENT NUMBER: 22152037 PubMed ID: 12162403
TITLE: Sildenafil improves right-ventricular parameters and quality of life in primary pulmonary hypertension.
AUTHOR: Zimmermann A T; Calvert A F; Veitch E M
SOURCE: Intern Med J, (2002 Aug) 32 (8) 424-6.
Journal code: 101092952. ISSN: 1444-0903.
PUB. COUNTRY: Australia
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20020807
Last Updated on STN: 20030111
Entered Medline: 20030110
CONTROLLED TERM: Check Tags: Case Report; Human; Male
Administration, Oral
Adult
Blood Gas Analysis
Dose-Response Relationship, Drug
Drug Administration Schedule
Follow-Up Studies
Heart Function Tests
Hypertension, Pulmonary: CO, complications
***Hypertension, Pulmonary: DT, drug therapy**
Hypertension, Pulmonary: US, ultrasonography
*Piperazines: AD, administration & dosage
Treatment Outcome
Ultrasonography, Doppler
*Ventricular Dysfunction, Right: DT, drug therapy
Ventricular Dysfunction, Right: ET, etiology
Ventricular Dysfunction, Right: US, ultrasonography
CAS REGISTRY NO.: **139755-83-2 (sildenafil)**
CHEMICAL NAME: 0 (Piperazines)

L46 ANSWER 33 OF 63 MEDLINE
ACCESSION NUMBER: 2002607920 MEDLINE
DOCUMENT NUMBER: 22254111 PubMed ID: 12368555
TITLE: Viagra neonatal experimentation - the Pandora's box!.
AUTHOR: Lewin Sanjiv
SOURCE: INDIAN PEDIATRICS, (2002 Sep) 39 (9) 894-5.
Journal code: 2985062R. ISSN: 0019-6061.
PUB. COUNTRY: India
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20021008
Last Updated on STN: 20021026
Entered Medline: 20021025
CONTROLLED TERM: Check Tags: Human

*Ethics, Medical
*Human Experimentation
Infant, Newborn
***Persistent Fetal Circulation Syndrome: DT, drug therapy**
*Piperazines: TU, therapeutic use
*Vasodilator Agents: TU, therapeutic use
CAS REGISTRY NO.: **139755-83-2 (sildenafil)**
CHEMICAL NAME: 0 (Piperazines); 0 (Vasodilator Agents)

L46 ANSWER 34 OF 63 MEDLINE
ACCESSION NUMBER: 2002673015 MEDLINE
DOCUMENT NUMBER: 22320891 PubMed ID: 12433774
TITLE: Sildenafil for "blue babies". Such unlicensed drug use might be justified as last resort.
COMMENT: Comment on: BMJ. 2002 Jul 27;325(7357):181
AUTHOR: Oliver James; Webb David J
SOURCE: BMJ (CLINICAL RESEARCH ED.), (2002 Nov 16) 325 (7373) 1174. Journal code: 8900488. ISSN: 1468-5833.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Commentary
Letter
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20021116
Last Updated on STN: 20021217
Entered Medline: 20021212
CONTROLLED TERM: Check Tags: Human
Drug Labeling
***Hypertension, Pulmonary: DT, drug therapy**
India
Infant
Infant, Newborn
*Phosphodiesterase Inhibitors: TU, therapeutic use
*Piperazines: TU, therapeutic use
*Vasodilator Agents: TU, therapeutic use
CAS REGISTRY NO.: **139755-83-2 (sildenafil)**
CHEMICAL NAME: 0 (Phosphodiesterase Inhibitors); 0 (Piperazines); 0 (Vasodilator Agents)

L46 ANSWER 35 OF 63 MEDLINE
ACCESSION NUMBER: 2002492028 MEDLINE
DOCUMENT NUMBER: 22242406 PubMed ID: 12354465
TITLE: Pulmonary hypertension and the search for the selective pulmonary vasodilator.
COMMENT: Comment on: Lancet. 2002 Sep 21;360(9337):895-900
Comment in: Lancet. 2003 Jan 4;361(9351):87
Erratum in: Lancet 2002 Dec 14;360(9349):1990
AUTHOR: Dweik Raed A
CORPORATE SOURCE: Department of Pulmonary and Critical Care Medicine, Cleveland Clinic Foundation, Cleveland, OH 44195, USA.. dweikr@ccf.org
SOURCE: LANCET, (2002 Sep 21) 360 (9337) 886-7. Journal code: 2985213R. ISSN: 0140-6736.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Commentary
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20021001
Last Updated on STN: 20030124

Searched by Barb O'Bryen, STIC 308-4291

[redacted]

Entered Medline: 20021016
CONTROLLED TERM: Check Tags: Female; Human; Male
Administration, Oral
***Hypertension, Pulmonary: DT, drug therapy**
*Nitric Oxide: PH, physiology
Nitric Oxide: TU, therapeutic use
*Piperazines: TU, therapeutic use
*Vasodilator Agents: TU, therapeutic use
CAS REGISTRY NO.: 10102-43-9 (Nitric Oxide); **139755-83-2 (sildenafil)**
CHEMICAL NAME: 0 (Piperazines); 0 (Vasodilator Agents)

L46 ANSWER 36 OF 63 MEDLINE
ACCESSION NUMBER: 2002393622 MEDLINE
DOCUMENT NUMBER: 22137449 PubMed ID: 12142299
TITLE: Indian doctor in protest after using Viagra to save "blue babies".
COMMENT: Comment in: BMJ. 2002 Nov 16;325(7373):1174
Comment in: BMJ. 2002 Nov 16;325(7373):1174
AUTHOR: Kumar Sanjay
SOURCE: BMJ (CLINICAL RESEARCH ED.), (2002 Jul 27) 325 (7357) 181.
Journal code: 8900488. ISSN: 1468-5833.
Report No.: KIE-105660.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: News Announcement
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Bioethics; Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020727
Last Updated on STN: 20030204
Entered Medline: 20020829
SUPPLEMENTARY TERM: Clinical Approach/Source; Professional Patient Relationship
CONTROLLED TERM: Check Tags: Human
Drug Labeling
***Hypertension, Pulmonary: DT, drug therapy**
India
Infant, Newborn
*Piperazines: TU, therapeutic use
*Vasodilator Agents: TU, therapeutic use
CAS REGISTRY NO.: **139755-83-2 (sildenafil)**
CHEMICAL NAME: 0 (Piperazines); 0 (Vasodilator Agents)

L46 ANSWER 37 OF 63 MEDLINE
ACCESSION NUMBER: 2002674064 MEDLINE
DOCUMENT NUMBER: 22321856 PubMed ID: 12434819
TITLE: Sildenafil for "blue babies". Ethics, conscience, and science have to be balanced against limited resources.
COMMENT: Comment on: BMJ. 2002 Jul 27;325(7357):181
AUTHOR: Patole Sanjay; Travadi Javeed
SOURCE: BMJ (CLINICAL RESEARCH ED.), (2002 Nov 16) 325 (7373) 1174.
Journal code: 8900488. ISSN: 1468-5833.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Commentary
Letter
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20021119
Last Updated on STN: 20021217
Entered Medline: 20021212
CONTROLLED TERM: Check Tags: Human
Drug Labeling
Ethics, Medical

***Hypertension, Pulmonary: DT, drug therapy**
India
Infant
Infant, Newborn
*Phosphodiesterase Inhibitors: TU, therapeutic use
*Piperazines: TU, therapeutic use
*Vasodilator Agents: TU, therapeutic use
CAS REGISTRY NO.: **139755-83-2 (sildenafil)**
CHEMICAL NAME: 0 (Phosphodiesterase Inhibitors); 0 (Piperazines); 0 (Vasodilator Agents)

L46 ANSWER 38 OF 63 MEDLINE
ACCESSION NUMBER: 2002427446 MEDLINE
DOCUMENT NUMBER: 22171486 PubMed ID: 12184280
TITLE: Long-term treatment with sildenafil in a thalassemic patient with pulmonary hypertension.
AUTHOR: Littera Roberto; La Nasa Giorgio; Derchi Giorgio; Cappellini Maria D; Chang Christy Y P; Contu Licinio
SOURCE: BLOOD, (2002 Aug 15) 100 (4) 1516-7.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020820
Last Updated on STN: 20020913
Entered Medline: 20020912
CONTROLLED TERM: Check Tags: Case Report; Human; Male
Adult
***Hypertension, Pulmonary: DT, drug therapy**
***Hypertension, Pulmonary: ET, etiology**
*Piperazines: AD, administration & dosage
*Vasodilator Agents: AD, administration & dosage
*beta-Thalassemia: CO, complications
CAS REGISTRY NO.: **139755-83-2 (sildenafil)**
CHEMICAL NAME: 0 (Piperazines); 0 (Vasodilator Agents)

L46 ANSWER 39 OF 63 MEDLINE
ACCESSION NUMBER: 2002381120 MEDLINE
DOCUMENT NUMBER: 22121944 PubMed ID: 12131202
TITLE: Sildenafil as a successful treatment of otherwise fatal HIV-related pulmonary hypertension.
AUTHOR: Carlsen Jorn; Kjeldsen Keld; Gerstoft Jan
SOURCE: AIDS, (2002 Jul 26) 16 (11) 1568-9.
Journal code: 8710219. ISSN: 0269-9370.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20020720
Last Updated on STN: 20021217
Entered Medline: 20021204
CONTROLLED TERM: Check Tags: Case Report; Female; Human
*HIV Infections: CO, complications
***Hypertension, Pulmonary: CO, complications**
***Hypertension, Pulmonary: DT, drug therapy**
Hypertension, Pulmonary: PP, physiopathology
Middle Age
Piperazines: PD, pharmacology
*Piperazines: TU, therapeutic use
CAS REGISTRY NO.: **139755-83-2 (sildenafil)**

CHEMICAL NAME: 0 (Piperazines)

L46 ANSWER 40 OF 63 MEDLINE
ACCESSION NUMBER: 2002219004 MEDLINE
DOCUMENT NUMBER: 21952258 PubMed ID: 11956051
TITLE: Intravenous sildenafil lowers pulmonary vascular resistance in a model of neonatal pulmonary hypertension.
AUTHOR: Shekerdemian Lara S; Ravn Hanne B; Penny Daniel J
CORPORATE SOURCE: Department of Cardiac Intensive Care, Great Ormond Street Hospital, London, United Kingdom..
shekel@cryptic.rch.unimelb.edu.au
SOURCE: AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, (2002 Apr 15) 165 (8) 1098-102.
Journal code: 9421642. ISSN: 1073-449X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020417
Last Updated on STN: 20020510
Entered Medline: 20020509

ABSTRACT:
Persistent pulmonary hypertension secondary to meconium aspiration syndrome is an important cause of morbidity and mortality in the neonatal population. We investigated the use of the phosphodiesterase-5 inhibitor sildenafil, in its intravenous form, as a pulmonary vasodilator in a model of meconium aspiration syndrome. Pulmonary hypertension was induced in 18 piglets, by endotracheal instillation of human meconium, 6 piglets subsequently received an infusion of intravenous sildenafil for 2 hours, 6 received inhaled nitric oxide for 2 hours, and 6 control animals received no additional intervention. Meconium aspiration increased pulmonary vascular resistance by 70%, and increased oxygenation index by over 100%. Pulmonary vascular resistance remained elevated for the remainder of the study period in control animals. Inhaled nitric oxide reduced the pulmonary vascular resistance by 40% after 2 hours of treatment; intravenous sildenafil completely reversed the increase in pulmonary vascular resistance within 1 hour of commencing the infusion. Neither agent had an effect on systemic hemodynamics. Sildenafil also increased cardiac output by 30%, but while doing so did not adversely influence oxygenation. Intravenous sildenafil is a selective and highly effective pulmonary vasodilator, which is at least as effective as inhaled nitric oxide, in this model of neonatal persistent pulmonary hypertension.

CONTROLLED TERM: Check Tags: Animal; Human; Support, Non-U.S. Gov't
Administration, Inhalation
Hemodynamics: DE, drug effects
Infant, Newborn
Infusions, Intravenous
Meconium Aspiration: CO, complications
Nitric Oxide: AD, administration & dosage
***Persistent Fetal Circulation Syndrome: DT, drug therapy**
Persistent Fetal Circulation Syndrome: ET, etiology
Persistent Fetal Circulation Syndrome: PP, physiopathology
*Phosphodiesterase Inhibitors: AD, administration & dosage
*Piperazines: AD, administration & dosage
*Pulmonary Circulation: DE, drug effects
Pulmonary Wedge Pressure: DE, drug effects
Swine
***Vascular Resistance: DE, drug effects**
Vasodilator Agents: AD, administration & dosage

CAS REGISTRY NO.: 10102-43-9 (Nitric Oxide); **139755-83-2 (sildenafil)**
CHEMICAL NAME: 0 (Phosphodiesterase Inhibitors); 0 (Piperazines); 0 (Vasodilator Agents)

L46 ANSWER 41 OF 63 MEDLINE
ACCESSION NUMBER: 2002492033 MEDLINE
DOCUMENT NUMBER: 22242411 PubMed ID: 12354470
TITLE: Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial.
COMMENT: Comment in: Lancet. 2002 Sep 21;360(9337):886-7
Comment in: Lancet. 2003 Jan 18;361(9353):262-3; author reply 263
AUTHOR: Ghofrani Hossein Ardeschir; Wiedemann Ralph; Rose Frank; Schermuly Ralph T; Olschewski Horst; Weissmann Norbert; Gunther Andreas; Walmrath Dieter; Seeger Werner; Grimminger Friedrich
CORPORATE SOURCE: Department of Internal Medicine, University Hospital, Justus-Liebig-University, 35392 Giessen, Germany.
SOURCE: LANCET, (2002 Sep 21) 360 (9337) 895-900.
Journal code: 2985213R. ISSN: 0140-6736.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20021001
Last Updated on STN: 20030206
Entered Medline: 20021016

ABSTRACT:
BACKGROUND: Lung fibrosis can be complicated by pulmonary hypertension, limiting exercise tolerance and life expectancy. Furthermore, vasodilators might cause deterioration in gas exchange. Our aim was to compare acute effects of sildenafil, nitric oxide, and epoprostenol in individuals with pulmonary hypertension secondary to lung fibrosis. METHODS: We did a randomised controlled, open-label trial, in 16 individuals admitted to our hospital with pulmonary hypertension secondary to lung fibrosis. After inhalation of nitric oxide (10-20 ppm), we assigned patients to either maximum tolerated dose of intravenous epoprostenol (mean 8.0 ng/kg per min; n=8) or oral sildenafil (50 mg; n=8). Our primary objective was to assess pulmonary vasodilative potency (decrease in pulmonary vascular resistance index) of sildenafil by comparison with inhaled nitric oxide and infused epoprostenol. Analyses were by intention to treat. FINDINGS: Pulmonary vascular resistance index was reduced by nitric oxide (-21.9%, 95% CI -14.1 to -36.2), epoprostenol (-36.9%, -24.4 to -59.6), and sildenafil (-32.5%, -10.2 to -54.1). However, ratio of pulmonary to systemic vascular resistance decreased only in individuals who received nitric oxide and sildenafil. Baseline measurement of multiple-inert-gas elimination showed right-to-left shunt flow (4.8%, 0.0-28.2) and little perfusion of low ventilation(V)/perfusion(Q) areas (0.1%, 0.0-13.0). Prostacyclin increased V/Q mismatch (shunt 16.8%, 10.8-35.9; low V/Q 3.8%, 0.0-13.0) and decreased arterial oxygenation. By contrast, nitric oxide (4.5%, 0.0-18.0; 0.0%, 0.0-17.3) and sildenafil (3.3%, 0.0-11.3; 0.0%, 0.0-12.4) maintained V/Q matching, with raised arterial partial pressure of oxygen (14.3 mm Hg, -1.7 to 31.3) noted for sildenafil. We recorded no adverse events. INTERPRETATION: Sildenafil causes preferential pulmonary vasodilation and improves gas exchange in patients with severe lung fibrosis and secondary pulmonary hypertension.

CONTROLLED TERM: Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Adult
Aged
Antihypertensive Agents: TU, therapeutic use
Epoprostenol: TU, therapeutic use

Searched by Barb O'Bryen, STIC 308-4291

Hemodynamics: DE, drug effects
***Hypertension, Pulmonary: DT, drug therapy**
Hypertension, Pulmonary: ET, etiology
Middle Age
*Nitric Oxide: TU, therapeutic use
*Piperazines: TU, therapeutic use
Pulmonary Fibrosis: CO, complications
*Pulmonary Fibrosis: DT, drug therapy
Pulmonary Gas Exchange: DE, drug effects
Vascular Resistance: DE, drug effects
*Vasodilator Agents: TU, therapeutic use
CAS REGISTRY NO.: 10102-43-9 (Nitric Oxide); **139755-83-2 (sildenafil)** ; 35121-78-9 (Epoprostenol)
CHEMICAL NAME: 0 (Antihypertensive Agents); 0 (Piperazines); 0 (Vasodilator Agents)

L46 ANSWER 42 OF 63 MEDLINE
ACCESSION NUMBER: 2002470323 MEDLINE
DOCUMENT NUMBER: 22217044 PubMed ID: 12231108
TITLE: Effect of sildenafil on the acute pulmonary vasodilator response to inhaled nitric oxide in adults with primary pulmonary hypertension.
AUTHOR: Lepore John J; Maroo Anjli; Pereira Naveen L; Ginns Leo C; Dec G William; Zapol Warren M; Bloch Kenneth D; Semigran Marc J
CORPORATE SOURCE: Cardiology Division, Cardiac Research Center, Pulmonary and Critical Care Unit and Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114, USA.
CONTRACT NUMBER: HL-04021 (NHLBI)
HL-42397 (NHLBI)
HL-57172 (NHLBI)
SOURCE: AMERICAN JOURNAL OF CARDIOLOGY, (2002 Sep 15) 90 (6) 677-80.
Journal code: 0207277. ISSN: 0002-9149.
PUB. COUNTRY: United States
DOCUMENT TYPE: (EVALUATION STUDIES)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20020917
Last Updated on STN: 20021024
Entered Medline: 20021023
CONTROLLED TERM: Check Tags: Comparative Study; Female; Human; Male; Support, U.S. Gov't, P.H.S.
Administration, Inhalation
Adult
Aged
Boston
Drug Therapy, Combination
***Hypertension, Pulmonary: DT, drug therapy**
*Lung: BS, blood supply
*Lung: DE, drug effects
Middle Age
*Nitric Oxide: TU, therapeutic use
Oxygen: TU, therapeutic use
*Piperazines: TU, therapeutic use
Pulmonary Wedge Pressure: DE, drug effects
Time Factors
Treatment Outcome
Vascular Resistance: DE, drug effects
Vasoconstriction: DE, drug effects

*Vasodilation: DE, drug effects
*Vasodilator Agents: TU, therapeutic use
Ventricular Pressure: DE, drug effects
CAS REGISTRY NO.: 10102-43-9 (Nitric Oxide); **139755-83-2 (sildenafil)** ; 7782-44-7 (Oxygen)
CHEMICAL NAME: 0 (Piperazines); 0 (Vasodilator Agents)

L46 ANSWER 43 OF 63 MEDLINE
ACCESSION NUMBER: 2002364867 MEDLINE
DOCUMENT NUMBER: 22102204 PubMed ID: 12107425
TITLE: Sildenafil in primary pulmonary hypertension--is there a subset of patients who respond favourably?.
AUTHOR: Sayin Tamer; Zenci Metin
CORPORATE SOURCE: Heart Centre, Ankara University, Ankara, Turkey.. tamsay@hotmail.com
SOURCE: CANADIAN JOURNAL OF CARDIOLOGY, (2002 Jun) 18 (6) 676-8. Journal code: 8510280. ISSN: 0828-282X.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020712
Last Updated on STN: 20020727
Entered Medline: 20020726

ABSTRACT:
Recently, case reports of patients with primary pulmonary hypertension (PPH) treated with sildenafil demonstrated encouraging results. The mechanism proposed is a relatively selective pulmonary vasodilation via increased levels of cGMP because of the inhibition of phosphodiesterase type 5. Two siblings with a similar medical history, severe symptoms and elevated levels of pulmonary artery pressures were diagnosed with PPH after a thorough diagnostic work-up. Both patients were treated with coumadin, sildenafil, furosemide, spironolactone and digoxin. One of the patients had no improvement during the hospital course and died two months after discharge. The other patient improved dramatically during the hospital course, and this improvement was sustained. At the three-month follow-up control, she was much improved in terms of clinical status and echocardiographic findings.

CONTROLLED TERM: Check Tags: Case Report; Female; Human; Male
Adolescence
Adult
Echocardiography
Fatal Outcome
Heart Catheterization
Heart Failure, Congestive: CO, complications
Heart Failure, Congestive: DI, diagnosis
Heart Failure, Congestive: US, ultrasonography
Hypertension, Pulmonary: CO, complications
Hypertension, Pulmonary: DI, diagnosis
***Hypertension, Pulmonary: DT, drug therapy**
*Piperazines: TU, therapeutic use
*Vasodilator Agents: TU, therapeutic use
CAS REGISTRY NO.: **139755-83-2 (sildenafil)**
CHEMICAL NAME: 0 (Piperazines); 0 (Vasodilator Agents)

L46 ANSWER 44 OF 63 MEDLINE
ACCESSION NUMBER: 2002444727 MEDLINE
DOCUMENT NUMBER: 22191833 PubMed ID: 12202882
TITLE: Sildenafil augments the effect of inhaled nitric oxide for postoperative pulmonary hypertensive crises.
AUTHOR: Atz Andrew M; Lefler Amy K; Fairbrother David L; Uber Walter E; Bradley Scott M

CORPORATE SOURCE: Division of Pediatric Cardiology, College of Pharmacy, and Division of Cardiothoracic Surgery, Medical University of South Carolina, Charleston, SC 29425, USA.. atzam@musc.edu
SOURCE: JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY, (2002 Sep) 124 (3) 628-9.
Journal code: 0376343. ISSN: 0022-5223.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20020831
Last Updated on STN: 20021010
Entered Medline: 20021009
CONTROLLED TERM: Check Tags: Case Report; Human; Male
Administration, Inhalation
Drug Synergism
Heart Valve Prosthesis Implantation
***Hypertension, Pulmonary: DT, drug therapy**
Hypertension, Pulmonary: ET, etiology
Infant
Mitral Valve Stenosis: CN, congenital
Mitral Valve Stenosis: SU, surgery
*Nitric Oxide: AD, administration & dosage
*Piperazines: PD, pharmacology
*Postoperative Complications: DT, drug therapy
Postoperative Complications: ET, etiology
Treatment Outcome
CAS REGISTRY NO.: 10102-43-9 (Nitric Oxide); **139755-83-2 (sildenafil)**
CHEMICAL NAME: 0 (Piperazines)

L46 ANSWER 45 OF 63 MEDLINE
ACCESSION NUMBER: 2002701006 MEDLINE
DOCUMENT NUMBER: 22348325 PubMed ID: 12462670
TITLE: A study of clinical efficacy of sildenafil in patients with primary pulmonary hypertension.
AUTHOR: Sastry B K S; Narasimhan C; Reddy N K; Anand B; Prakash G S; Raju P Raghava; Kumar D N
CORPORATE SOURCE: Department of Cardiology, CARE Hospitals and CARE Foundation, Hyderabad.. bkssastry@hotmail.com
SOURCE: INDIAN HEART JOURNAL, (2002 Jul-Aug) 54 (4) 410-4.
Journal code: 0374675. ISSN: 0019-4832.
PUB. COUNTRY: India
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20021217
Last Updated on STN: 20030208
Entered Medline: 20030207

ABSTRACT:
BACKGROUND: Primary pulmonary hypertension is a disorder with limited treatment options and poor outcome. Sildenafil, a pulmonary vasodilator, is likely to be beneficial in primary pulmonary hypertension. We studied the clinical efficacy of sildenafil in patients with primary pulmonary hypertension. METHODS AND RESULTS: A registry of patients with primary pulmonary hypertension has been maintained in our hospital since January 1999. Of a total of 60 patients. 29 (M:16, F:13) consented to try sildenafiL. New York Heart Association functional class, six-minute walk test and Doppler echocardiographic evaluation of pulmonary artery pressure was done before and after treatment with sildenafil. Sildenafil was initiated at a dose of 25 mg thrice a day and increased up to 100 mg thrice a day as tolerated. There was a significant improvement in the functional class. The six-minute walked distance increased from 297.07+/-130.69

m at baseline to 427.68+/-85.35 m after 3 months of sildenafil therapy (p<0.0003). The mean of the pulmonary artery systolic pressure before starting sildenaffil was 109.26+/-24.15 mmHg (mean+/-SD) and it decreased to 95.15+/-24.64 mmHg (p<0.008). While 19 of the 31 historical controls in whom sildenafil was not given died during follow-up (11-44 months), only 1 of the 29 patients given sildenafil died (in an accident) during follow-up (5-20 months). CONCLUSIONS: Sildenafil, a pulmonary vasodilator, has a beneficial effect in patients with primary pulmonary hypertension in improving the functional class, six-minute walked distance and in decreasing the pulmonary artery pressures.

CONTROLLED TERM: Check Tags: Female; Human; Male
Adolescent
Adult
Child
Child, Preschool
***Hypertension, Pulmonary: DT, drug therapy**
Middle Age
*Piperazines: TU, therapeutic use
Prospective Studies
Statistics, Nonparametric
Survival Analysis
*Vasodilator Agents: TU, therapeutic use
CAS REGISTRY NO.: **139755-83-2 (sildenafil)**
CHEMICAL NAME: 0 (Piperazines); 0 (Vasodilator Agents)

L46 ANSWER 46 OF 63 MEDLINE
ACCESSION NUMBER: 2002701005 MEDLINE
DOCUMENT NUMBER: 22348324 PubMed ID: 12462669
TITLE: Chronic oral sildenafil therapy in severe pulmonary artery hypertension.
AUTHOR: Kothari Shyam S; Duggal Bhanu
CORPORATE SOURCE: Cardiothoracic Centre, All India Institute of Medical Sciences, New Delhi.. kotharis@del2.vsnl.net.in
SOURCE: INDIAN HEART JOURNAL, (2002 Jul-Aug) 54 (4) 404-9. Journal code: 0374675. ISSN: 0019-4832.
PUB. COUNTRY: India
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20021217
Last Updated on STN: 20030208
Entered Medline: 20030207

ABSTRACT:
BACKGROUND: Sildenafil, a selective phosphor-diesterase-5 inhibitor, may be of clincal benefit in patients with pulmonary artery hypertension. METHODS AND RESULTS: Fourteen patients, aged 5-30 years, with severe pulmonary artery hypertension (9 with primary pulmonary hypertension, 5 with operated congenital heart disease) received oral sildenafil in addition to conventional therapy. Twelve patients were in New York Heart Association functional class III or IV. The drug was started in low dose and empirically increased. Finally a median dose of 87.5 mg/day was used in children weighing less than 30 kg, and 150 mg/day in those with weight more than 30 kg. The patients were followed up by assessing their functional status, six-minute walk test, Doppler echocardiography and hemodynamic study (in selected cases). On mean follow-up of 7.3+/-2.4 months (range 3-14 months), New York Heart Association functional class improved from 3.31+/-0.75 to 2.00+/-0.71 (p<0.002). There was a remarkable improvement on the six-minute walk test from a baseline of 264.1+/-193.7 m to 408.2+/-156.97 m at 3 months (p<0.001) and 453.2+/-159.81 (p<0.0001) at 6 months. The right ventricular systolic pressure estimated echocardiographically declined from 112.40+/-45.21 mmHg to 101.86+/-47.86 mmHg (p<0.002). The mean pulmonary artery pressure decreased from 62 mmHg to 47 mmHg in 4 patients of primary pulmonary hypertension recatheterized after a mean of

7 months of sildenafil treatment. Clinical improvement was seen even when no decrease in pulmonary artery pressure was demonstrated in one patient with secondary pulmonary artery hypertension. However, 2 patients died during follow-up despite clinical improvement. CONCLUSIONS: Oral sildenafil was well tolerated and led to an improved clinical condition and exercise performance. Whether the drug improves mortality remains to be established. Larger trials a rewarranted.

CONTROLLED TERM: Check Tags: Female; Human; Male
Administration, Oral
Adolescent
Adult
Child
Child, Preschool
***Hypertension, Pulmonary: DT, drug therapy**
*Piperazines: TU, therapeutic use
*Vasodilator Agents: TU, therapeutic use
CAS REGISTRY NO.: **139755-83-2 (sildenafil)**
CHEMICAL NAME: 0 (Piperazines); 0 (Vasodilator Agents)

L46 ANSWER 47 OF 63 MEDLINE
ACCESSION NUMBER: 2002271339 MEDLINE
DOCUMENT NUMBER: 22006343 PubMed ID: 12011826
TITLE: Sildenafil for primary and secondary pulmonary hypertension.
AUTHOR: Watanabe Hiroshi; Ohashi Kyoichi; Takeuchi Kazuhiko; Yamashita Kazuhiro; Yokoyama Taku; Tran Quang-Kim; Satoh Hiroshi; Terada Hajime; Ohashi Hiroyuki; Hayashi Hideharu
CORPORATE SOURCE: Department of Clinical Pharmacology and Therapeutics, Hamamatsu University School of Medicine, 1-20-1 Handayama, Hamamatsu 431-3192, Japan.. hwat@hama-med.ac.jp
SOURCE: CLINICAL PHARMACOLOGY AND THERAPEUTICS, (2002 May) 71 (5) 398-402.
Journal code: 0372741. ISSN: 0009-9236.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020516
Last Updated on STN: 20020618
Entered Medline: 20020617

ABSTRACT:
BACKGROUND: Sildenafil is a selective inhibitor of cyclic guanosine monophosphate-specific phosphodiesterase type 5, an enzyme that is abundant in both lung and penile tissues. Sildenafil is widely used to dilate penile arteries, suggesting that it may also dilate pulmonary arteries in patients with pulmonary hypertension. However, the long-term hemodynamic effects and safety of the drug in pulmonary hypertension are not known. METHODS: One patient with primary pulmonary hypertension and another with secondary pulmonary hypertension caused by collagen disease were given 50 mg oral sildenafil during cardiac catheterization for assessment of the acute hemodynamic effects of the drug. The patients were then given maintenance treatment with 25 mg oral sildenafil twice a day. Long-term hemodynamic effects were evaluated by repeated cardiac catheterization after 3 months, with the last oral dose given 15 hours before the procedure. The acute hemodynamic effects of sildenafil after the long-term treatment were studied during the same cardiac catheterization. RESULTS: Sildenafil did not affect aortic pressure, but it significantly decreased pulmonary artery pressure and increased cardiac index, thereby reducing pulmonary vascular resistance. Long-term maintenance therapy with 25 mg oral sildenafil twice a day remarkably improved the clinical condition of the patients, without causing any adverse effects; New York Heart Association functional classification returned to class

II (from class III). The acute efficacy of sildenafil was well preserved after the long-term treatment; there was no tolerance. CONCLUSIONS: The data strongly suggest that sildenafil can be used as a valuable pulmonary vasodilator in patients with pulmonary hypertension, with good long-term hemodynamic effects and safety. The results necessitate larger trials to confirm these observations in a larger cohort of patients.

CONTROLLED TERM: Check Tags: Case Report; Female; Human
3',5'-Cyclic-GMP Phosphodiesterase: AI, antagonists & inhibitors
Adult
***Hypertension, Pulmonary: DT, drug therapy**
Hypertension, Pulmonary: EN, enzymology
Hypertension, Pulmonary: PP, physiopathology
Middle Age
Piperazines: PD, pharmacology
*Piperazines: TU, therapeutic use
Pulmonary Wedge Pressure: DE, drug effects
Pulmonary Wedge Pressure: PH, physiology
Time
Vasodilator Agents: PD, pharmacology
*Vasodilator Agents: TU, therapeutic use
CAS REGISTRY NO.: **139755-83-2 (sildenafil)**
CHEMICAL NAME: 0 (Piperazines); 0 (Vasodilator Agents); EC 3.1.4.35 (3',5'-Cyclic-GMP Phosphodiesterase)

L46 ANSWER 48 OF 63 MEDLINE
ACCESSION NUMBER: 2002389030 MEDLINE
DOCUMENT NUMBER: 22132612 PubMed ID: 12137450
TITLE: Sildenafil for primary pulmonary hypertension: short and long-term symptomatic benefit.
AUTHOR: Jackson G; Chambers J
CORPORATE SOURCE: Cardiothoracic Centre, St Thomas' Hospital, London, UK.
SOURCE: INTERNATIONAL JOURNAL OF CLINICAL PRACTICE, (2002 Jun) 56 (5) 397-8.
Journal code: 9712381. ISSN: 1368-5031.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020725
Last Updated on STN: 20020914
Entered Medline: 20020913

ABSTRACT:
We report two cases of primary pulmonary hypertension (PPH) who benefited from oral sildenafil therapy. Both demonstrated a substantial improvement in exercise ability, which has been sustained at 3 and 6 months. Sildenafil acting as a phosphodiesterase 5 inhibitor may have an important role to play in the management of PPH and we believe further study to be of importance.

CONTROLLED TERM: Check Tags: Case Report; Female; Human; Male
Administration, Oral
Adult
Aged
***Hypertension, Pulmonary: DT, drug therapy**
*Phosphodiesterase Inhibitors: AD, administration & dosage
*Piperazines: AD, administration & dosage
Treatment Outcome
*Vasodilator Agents: AD, administration & dosage
CAS REGISTRY NO.: **139755-83-2 (sildenafil)**
CHEMICAL NAME: 0 (Phosphodiesterase Inhibitors); 0 (Piperazines); 0 (Vasodilator Agents)

L46 ANSWER 49 OF 63 MEDLINE
ACCESSION NUMBER: 2002458464 MEDLINE
DOCUMENT NUMBER: 22205086 PubMed ID: 12216929
TITLE: Sildenafil in the management of primary pulmonary hypertension.
AUTHOR: Singh Balbir; Gupta Ripen; Punj Vandana; Ghose Tapan; Sapra Rakesh; Grover D N; Kaul Upendra
CORPORATE SOURCE: Department of Interventional Cardiology, Batra Hospital and Medical Research Centre, New Delhi.
SOURCE: INDIAN HEART JOURNAL, (2002 May-Jun) 54 (3) 297-300.
Journal code: 0374675. ISSN: 0019-4832.
PUB. COUNTRY: India
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 20020910
Last Updated on STN: 20021212
Entered Medline: 20021108

ABSTRACT:
Primary pulmonary hypertension is a rare disorder of unknown etiology with a poor prognosis. There is no cure, and drug therapy is effective in only a few patients. Calcium-channel antagonists and anticoagulants are the mainstay of therapy. Prostacyclin therapy leads to significant clinical improvement but its use is restricted due to high cost and complex drug delivery systems. Sildenafil is a selective vasodilator and has been shown to be effective in decreasing pulmonary vascular resistance in animal models of pulmonary hypertension. We report the use of sildenafil in two patients of primary pulmonary hypertension who were refractory to conventional drug therapy.

CONTROLLED TERM: Check Tags: Case Report; Female; Human
Adult
***Hypertension, Pulmonary: DT, drug therapy**
*Phosphodiesterase Inhibitors: TU, therapeutic use
*Piperazines: TU, therapeutic use
Treatment Outcome
*Vasodilator Agents: TU, therapeutic use
CAS REGISTRY NO.: **139755-83-2 (sildenafil)**
CHEMICAL NAME: 0 (Phosphodiesterase Inhibitors); 0 (Piperazines); 0 (Vasodilator Agents)

L46 ANSWER 50 OF 63 MEDLINE
ACCESSION NUMBER: 2002271376 MEDLINE
DOCUMENT NUMBER: 22006388 PubMed ID: 12011667
TITLE: Recent advances in pulmonary vascular disease.
AUTHOR: Adatia Ian
CORPORATE SOURCE: Department of Critical Care Medicine, The Hospital for Sick Children, Toronto, Ontario, Canada.. ian.adatia@sickkids.ca
SOURCE: CURRENT OPINION IN PEDIATRICS, (2002 Jun) 14 (3) 292-7.
Ref: 69
Journal code: 9000850. ISSN: 1040-8703.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020516
Last Updated on STN: 20020718
Entered Medline: 20020717

ABSTRACT:

There have been remarkable advances in our understanding of the pathobiology of pulmonary hypertension. A region on chromosome 2 encoding bone morphogenetic receptor type 2 has been identified to underlie familial and many cases of sporadic primary pulmonary arterial hypertension. The vasoactive mediators, discovered and defined by vascular biologists, have been translated into promising treatments of human disease. Prostacyclin, endothelin receptor blockers, sildenafil, and nitric oxide have been applied therapeutically to limit, and occasionally reverse, the inexorable damage to the pulmonary circulation initiated by recently identified genetic and environmental triggers of pulmonary arterial hypertension.

CONTROLLED TERM: Check Tags: Human
*Antihypertensive Agents: TU, therapeutic use
*Bronchodilator Agents: TU, therapeutic use
Child
Chromosomes, Human, Pair 2
Eisenmenger Complex: GE, genetics
Epoprostenol: TU, therapeutic use
***Hypertension, Pulmonary: DT, drug therapy**
Hypertension, Pulmonary: GE, genetics
Mutation
Nitric Oxide: TU, therapeutic use
Piperazines: TU, therapeutic use
Protein-Serine-Threonine Kinases: GE, genetics
Pulmonary Artery: PP, physiopathology
Receptors, Endothelin: TU, therapeutic use
Transforming Growth Factor beta: ME, metabolism
*Vasodilator Agents: TU, therapeutic use

CAS REGISTRY NO.: 10102-43-9 (Nitric Oxide); **139755-83-2 (sildenafil)** ; 35121-78-9 (Epoprostenol)

CHEMICAL NAME: 0 (Antihypertensive Agents); 0 (Bronchodilator Agents); 0 (Piperazines); 0 (Receptors, Endothelin); 0 (Transforming Growth Factor beta); 0 (Vasodilator Agents); EC 2.7.1.- (BMP type II receptor); EC 2.7.1.- (Protein-Serine-Threonine Kinases)

L46 ANSWER 51 OF 63 MEDLINE

ACCESSION NUMBER: 2002464017 MEDLINE

DOCUMENT NUMBER: 22211313 PubMed ID: 12223337

TITLE: [The combined use of sildenafil with epoprostenol in a patient with primary pulmonary hypertension]. Primer pulmoner hipertansiyonlu bir olguda kombine sildenafil ve epoprostenol kullanimi.

AUTHOR: Kayikcioglu Meral; Can Levent H; Payzin Serdar; Kultursay Hakan; Soydan Inan

CORPORATE SOURCE: Department of Cardiology, Medical Faculty, Ege University, Izmir.. mekay@med.ege.edu.tr

SOURCE: Anadolu Kardiyol Derg, (2002 Sep) 2 (3) 262-4. Journal code: 101095069. ISSN: 1302-8723.

PUB. COUNTRY: Turkey

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: Turkish

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200212

ENTRY DATE: Entered STN: 20020912
Last Updated on STN: 20021227
Entered Medline: 20021224

CONTROLLED TERM: Check Tags: Case Report; Female; Human
Adult
Antihypertensive Agents: AD, administration & dosage
*Antihypertensive Agents: TU, therapeutic use
Drug Therapy, Combination
Echocardiography

Electrocardiography
Epoprostenol: AD, administration & dosage
*Epoprostenol: TU, therapeutic use
***Hypertension, Pulmonary: DT, drug therapy**
Hypertension, Pulmonary: US, ultrasonography
Piperazines: AD, administration & dosage
*Piperazines: TU, therapeutic use
Vasodilator Agents: AD, administration & dosage
*Vasodilator Agents: TU, therapeutic use
CAS REGISTRY NO.: **139755-83-2 (sildenafil)**; 35121-78-9 (Epoprostenol)
CHEMICAL NAME: 0 (Antihypertensive Agents); 0 (Piperazines); 0 (Vasodilator Agents)

L46 ANSWER 52 OF 63 MEDLINE
ACCESSION NUMBER: 2003019378 MEDLINE
DOCUMENT NUMBER: 22413878 PubMed ID: 12525997
TITLE: Emerging medical therapies for pulmonary arterial hypertension.
AUTHOR: Galie Nazzareno; Manes Alessandra; Branzi Angelo
CORPORATE SOURCE: Institute of Cardiology, University of Bologna, Italy.
SOURCE: PROGRESS IN CARDIOVASCULAR DISEASES, (2002 Nov-Dec) 45 (3) 213-24. Ref: 70
Journal code: 0376442. ISSN: 0033-0620.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20030115
Last Updated on STN: 20030129
Entered Medline: 20030128

ABSTRACT:
Until a few years ago, "conventional" treatment for pulmonary arterial hypertension (PAH) included oral anticoagulants, calcium channel blockers, diuretics, digoxin, and oxygen. In the 1990s, 3 randomized studies demonstrated that the continuous intravenous infusion of epoprostenol improved functional capacity, cardiopulmonary hemodynamics, and survival in patients with severe PAH. Recently, the thromboxane inhibitor terbogrel, the prostacyclin analogues treprostinil, beraprost, and iloprost, and the endothelin receptor antagonist bosentan have been tested in clinical trials in more than 1,100 patients. Except for terbogrel, all compounds have improved by different degrees the mean exercise capacity as assessed by 6 minutes walking distance. Conversely, these trials differ for the severity and etiology of included PAH patients as well as for the effects on combined clinical events, on quality of life, and on hemodynamics. No trials have shown effects on mortality, and each new compound presents different side effects that seem unpredictable in the individual patient. At present, additional new compounds such as sitaxentan, ambisentan, L-arginine, and sildenafil are studied in clinical trials. The new therapeutic options are currently in different phases of approval by regulatory agencies, and when they will become available we will have the opportunity to select the most appropriate treatment for the single patient, according to an individualized benefit-to-risk ratio.

CONTROLLED TERM: Check Tags: Human
Arginine: TU, therapeutic use
Controlled Clinical Trials
Drug Therapy, Combination
Endothelin-1: ME, metabolism
Endothelium, Vascular: DE, drug effects

Endothelium, Vascular: PP, physiopathology
*Epoprostenol: AA, analogs & derivatives
Epoprostenol: ME, metabolism
Epoprostenol: TU, therapeutic use
***Hypertension, Pulmonary: DT, drug therapy**
Hypertension, Pulmonary: ME, metabolism
Hypertension, Pulmonary: PP, physiopathology
Iloprost: TU, therapeutic use
Nitric Oxide: ME, metabolism
Piperazines: TU, therapeutic use
Platelet Aggregation Inhibitors: TU, therapeutic use
Pyridines: TU, therapeutic use
Signal Transduction: DE, drug effects
Sulfonamides: TU, therapeutic use
Thromboxane A2: ME, metabolism
Vasodilator Agents: TU, therapeutic use

CAS REGISTRY NO.: 10102-43-9 (Nitric Oxide); **139755-83-2 (sildenafil)** ; 147536-97-8 (bosentan); 149979-74-8 (terbogrel); 35121-78-9 (Epoprostenol); 57576-52-0 (Thromboxane A2); 74-79-3 (Arginine); 78919-13-8 (Iloprost); 88430-50-6 (beraprost)

CHEMICAL NAME: 0 (Endothelin-1); 0 (Piperazines); 0 (Platelet Aggregation Inhibitors); 0 (Pyridines); 0 (Sulfonamides); 0 (UT15 compound); 0 (Vasodilator Agents)

L46 ANSWER 53 OF 63 MEDLINE
ACCESSION NUMBER: 2002365485 MEDLINE
DOCUMENT NUMBER: 22103435 PubMed ID: 12107399
TITLE: Developments in therapeutics for pulmonary arterial hypertension.
AUTHOR: Wilkins M R; Moller G M O; Ren X; Wharton J
CORPORATE SOURCE: Section on Clinical Pharmacology Imperial College, Hammersmith Hospital, London, UK.. m.wilkins@ic.ac.uk
SOURCE: MINERVA CARDIOANGIOLOGICA, (2002 Jun) 50 (3) 175-87. Ref: 77
Journal code: 0400725. ISSN: 0026-4725.
PUB. COUNTRY: Italy
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 20020712
Last Updated on STN: 20021212
Entered Medline: 20021115

ABSTRACT:
For many years, the management of pulmonary hypertension has been frustrated by an inadequate understanding of its pathology and limited therapeutic options, but this is changing rapidly. Recently, novel insight into the pathogenesis of primary pulmonary hypertension (PPH) has been provided by the demonstration of mutations in BMPR2 and ALK-1 genes in a significant number of patients with the condition. These genes encode members of the TGF-b receptor superfamily and their integrity is important in the maintenance of normal pulmonary vascular structure and function. At the same time, there has been a major advance in the treatment of the condition due to development of 2 orally active pharmacological agents, bosentan and sildenafil, which demonstrate some selectivity for the pulmonary vasculature. This review examines how the management of PPH and severe pulmonary hypertension in associated diseases has changed and looks at exciting future developments.

CONTROLLED TERM: Check Tags: Comparative Study; Human
*Antihypertensive Agents: TU, therapeutic use

Endothelins: AI, antagonists & inhibitors
Endothelins: PH, physiology
Forecasting
Gene Therapy
Genotype
Hypertension, Pulmonary: DT, drug therapy
Hypertension, Pulmonary: GE, genetics
Hypertension, Pulmonary: PP, physiopathology
***Hypertension, Pulmonary: TH, therapy**
Mutation
*Phosphodiesterase Inhibitors: TU, therapeutic use
*Piperazines: TU, therapeutic use
Polymorphism (Genetics)
Receptors, Transforming Growth Factor beta: GE, genetics
Serotonin: GE, genetics
Serotonin: PH, physiology
*Sulfonamides: TU, therapeutic use
Transcription, Genetic
*Vasodilator Agents: TU, therapeutic use

CAS REGISTRY NO.: **139755-83-2 (sildenafil)**; 147536-97-8 (bosentan); 50-67-9 (Serotonin)
CHEMICAL NAME: 0 (Antihypertensive Agents); 0 (Endothelins); 0 (Phosphodiesterase Inhibitors); 0 (Piperazines); 0 (Receptors, Transforming Growth Factor beta); 0 (Sulfonamides); 0 (Vasodilator Agents)

L46 ANSWER 54 OF 63 MEDLINE
ACCESSION NUMBER: 2002196632 MEDLINE
DOCUMENT NUMBER: 21924380 PubMed ID: 11926808
TITLE: Summary for patients. Sildenafil (Viagra) may help improve control of pulmonary hypertension.
COMMENT: Original report in: Ann Intern Med. 2002 Apr 2;136(7):515-22
AUTHOR: Anonymous
SOURCE: ANNALS OF INTERNAL MEDICINE, (2002 Apr 2) 136 (7) I35. Journal code: 0372351. ISSN: 1539-3704.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(PATIENT EDUCATION HANDOUT)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020404
Last Updated on STN: 20020424
Entered Medline: 20020423
CONTROLLED TERM: Check Tags: Female; Human; Male
*3',5'-Cyclic-GMP Phosphodiesterase: AI, antagonists & inhibitors
Administration, Oral
Dose-Response Relationship, Drug
Drug Synergism
Drug Therapy, Combination
***Hypertension, Pulmonary: DT, drug therapy**
*Iloprost: AD, administration & dosage
Iloprost: PK, pharmacokinetics
*Phosphodiesterase Inhibitors: AD, administration & dosage
*Piperazines: AD, administration & dosage
*Vasodilator Agents: AD, administration & dosage

CAS REGISTRY NO.: **139755-83-2 (sildenafil)**; 78919-13-8 (Iloprost)
CHEMICAL NAME: 0 (Phosphodiesterase Inhibitors); 0 (Piperazines); 0 (Vasodilator Agents); EC 3.1.4.35 (3',5'-Cyclic-GMP Phosphodiesterase)

L46 ANSWER 55 OF 63 MEDLINE
ACCESSION NUMBER: 2001294200 MEDLINE
DOCUMENT NUMBER: 21272179 PubMed ID: 11378627
TITLE: Therapy of pulmonary hypertension: targeting pathogenic mechanisms with selective treatment delivery.
COMMENT: Comment on: Crit Care Med. 2001 May;29(5):1000-5
AUTHOR: Rubin L J
SOURCE: CRITICAL CARE MEDICINE, (2001 May) 29 (5) 1086-7.
Journal code: 0355501. ISSN: 0090-3493.
PUB. COUNTRY: United States
DOCUMENT TYPE: Commentary
Editorial
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010618
Last Updated on STN: 20010618
Entered Medline: 20010614
CONTROLLED TERM: Check Tags: Human
Drug Synergism
***Hypertension, Pulmonary: DT, drug therapy**
Nitric Oxide: TU, therapeutic use
*Phosphodiesterase Inhibitors: TU, therapeutic use
*Piperazines: TU, therapeutic use
Vasodilation: DE, drug effects
CAS REGISTRY NO.: 10102-43-9 (Nitric Oxide); **139755-83-2 (sildenafil)**
CHEMICAL NAME: 0 (Phosphodiesterase Inhibitors); 0 (Piperazines)

L46 ANSWER 56 OF 63 MEDLINE
ACCESSION NUMBER: 2001182721 MEDLINE
DOCUMENT NUMBER: 21109253 PubMed ID: 11179097
TITLE: Viagra for impotence of pulmonary vasodilator therapy?.
COMMENT: Comment on: Am J Respir Crit Care Med. 2001 Feb;163(2):339-43
AUTHOR: Lodato R F
SOURCE: AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, (2001 Feb) 163 (2) 312-3.
Journal code: 9421642. ISSN: 1073-449X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Commentary
Editorial
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010329
CONTROLLED TERM: Check Tags: Human
Hemodynamics: DE, drug effects
***Hypertension, Pulmonary: DT, drug therapy**
*Phosphodiesterase Inhibitors: TU, therapeutic use
*Piperazines: TU, therapeutic use
*Vasodilator Agents: TU, therapeutic use
CAS REGISTRY NO.: **139755-83-2 (sildenafil)**
CHEMICAL NAME: 0 (Phosphodiesterase Inhibitors); 0 (Piperazines); 0 (Vasodilator Agents)

L46 ANSWER 57 OF 63 MEDLINE
ACCESSION NUMBER: 2001497958 MEDLINE
DOCUMENT NUMBER: 21430582 PubMed ID: 11546958
TITLE: Sildenafil in HIV-related pulmonary hypertension.
AUTHOR: Schumacher Y O; Zdebik A; Huonker M; Kreisel W

SOURCE: AIDS, (2001 Sep 7) 15 (13) 1747-8.
Journal code: 8710219. ISSN: 0269-9370.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20010910
Last Updated on STN: 20020222
Entered Medline: 20011207
CONTROLLED TERM: Check Tags: Case Report; Female; Human; Male
Adult
*HIV Infections: CO, complications
***Hypertension, Pulmonary: DT, drug therapy**
Hypertension, Pulmonary: ET, etiology
*Phosphodiesterase Inhibitors: TU, therapeutic use
*Piperazines: TU, therapeutic use
CAS REGISTRY NO.: **139755-83-2 (sildenafil)**
CHEMICAL NAME: 0 (Phosphodiesterase Inhibitors); 0 (Piperazines)

L46 ANSWER 58 OF 63 MEDLINE
ACCESSION NUMBER: 2001668057 MEDLINE
DOCUMENT NUMBER: 21538472 PubMed ID: 11682443
TITLE: Clonidine-induced nitric oxide-dependent vasorelaxation mediated by endothelial alpha(2)-adrenoceptor activation.
AUTHOR: Figueroa X F; Poblete M I; Boric M P; Mendizabal V E; Adler-Graschinsky E; Huidobro-Toro J P
CORPORATE SOURCE: Unidad de Regulacion Neurohumoral, Departamento de Ciencias Fisiologicas, Facultad de Ciencias Biologicas, Pontificia Universidad Catolica de Chile, Santiago, Chile.
SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (2001 Nov) 134 (5) 957-68.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011121
Last Updated on STN: 20020123
Entered Medline: 20011207

ABSTRACT:
1. To assess the involvement of endothelial alpha(2)-adrenoceptors in the clonidine-induced vasodilatation, the mesenteric artery of Sprague Dawley rats was cannulated and perfused with Tyrode solution (2 ml min(-1)). We measured perfusion pressure, nitric oxide (NO) in the perfusate using chemiluminescence, and tissue cyclic GMP by RIA. 2. In phenylephrine-precontracted mesenteries, clonidine elicited concentration-dependent vasodilatations associated to a rise in luminal NO. One hundred nM rauwolscine or 100 microM L(omega)-nitro-L-arginine antagonized the clonidine-induced vasodilatation. Guanabenz, guanfacine, and oxymetazoline mimicked the clonidine-induced vasorelaxation. 3. In non-contracted mesenteries, 100 nM clonidine elicited a maximal rise of NO (123+/-13 pmol); associated to a peak in tissue cyclic GMP. Endothelium removal, L(omega)-nitro-L-arginine, or rauwolscine ablated the rise in NO. One hundred nM aminoclonidine, guanfacine, guanabenz, UK14,304 and oxymetazoline mimicked the clonidine-induced surge of NO. Ten microM ODQ obliterated the clonidine-induced vasorelaxation and the associated tissue cyclic GMP accumulation; 10 - 100 nM sildenafil increased tissue cyclic GMP accumulation without altering the clonidine-induced NO release. 4. alpha(2)-Adrenergic blockers antagonized the clonidine-induced rise in NO. Consistent with a preferential alpha(2D)-adrenoceptor activation, the K(B)s for yohimbine, rauwolscine, phentolamine, WB-4101, and prazosin were: 6.8, 24, 19, 165, and 1489 nM, respectively. 5. Rat pretreatment with 100 mg kg(-1) 6-hydroxydopamine reduced 95% tissue noradrenaline and 60% neuropeptide Y. In these preparations,

100 nM clonidine elicited a rise of 91.9+/-15.5 pmol NO. Perfusion with 1 microM guanethidine or 1 microM guanethidine plus 1 microM atropine did not modify the NO surge evoked by 100 nM clonidine. 6. Clonidine and congeners activate endothelial alpha(2D)-adrenoceptors coupled to the L-arginine pathway, suggesting that the antihypertensive action of clonidine involves an endothelial vasorelaxation mediated by NO release, in addition to presynaptic mechanisms.

CONTROLLED TERM: Check Tags: Animal; Comparative Study; In Vitro; Support, Non-U.S. Gov't
Acetylcholine: PD, pharmacology
*Adrenergic alpha-Agonists: PD, pharmacology
Adrenergic alpha-Antagonists: PD, pharmacology
*Clonidine: PD, pharmacology
Cyclic GMP: ME, metabolism
Dose-Response Relationship, Drug
Endothelium, Vascular: DE, drug effects
Endothelium, Vascular: ME, metabolism
Enzyme Inhibitors: PD, pharmacology
Guanylate Cyclase: AI, antagonists & inhibitors
Guanylate Cyclase: ME, metabolism
Mesenteric Arteries: DE, drug effects
Mesenteric Arteries: ME, metabolism
Mesenteric Arteries: PH, physiology
Nitric Oxide: ME, metabolism
*Nitric Oxide: PH, physiology
Nitroarginine: PD, pharmacology
Oxadiazoles: PD, pharmacology
Oxidopamine: PD, pharmacology
Phenylephrine: PD, pharmacology
Phosphodiesterase Inhibitors: PD, pharmacology
Phosphoric Diester Hydrolases: ME, metabolism
Piperazines: PD, pharmacology
Quinoxalines: PD, pharmacology
Rats
Rats, Sprague-Dawley
*Receptors, Adrenergic, alpha-2: DE, drug effects
Receptors, Adrenergic, alpha-2: ME, metabolism
Saponins: PD, pharmacology
Solubility
Sympatholytics: PD, pharmacology
Time Factors
Vascular Resistance
*Vasodilation: DE, drug effects
Vasodilator Agents: PD, pharmacology
Yohimbine: PD, pharmacology

CAS REGISTRY NO.: 10102-43-9 (Nitric Oxide); 1199-18-4 (Oxidopamine); **139755-83-2 (sildenafil)**; 146-48-5 (Yohimbine); 2149-70-4 (Nitroarginine); 4205-90-7 (Clonidine); 51-84-3 (Acetylcholine); 59-42-7 (Phenylephrine); 7665-99-8 (Cyclic GMP)

CHEMICAL NAME: 0 (1H-(1,2,4)oxadiazolo(4,3-a)quinoxalin-1-one); 0 (Adrenergic alpha-Agonists); 0 (Adrenergic alpha-Antagonists); 0 (Enzyme Inhibitors); 0 (Oxadiazoles); 0 (Phosphodiesterase Inhibitors); 0 (Piperazines); 0 (Quinoxalines); 0 (Receptors, Adrenergic, alpha-2); 0 (Saponins); 0 (Sympatholytics); 0 (Vasodilator Agents); EC 3.1.4 (Phosphoric Diester Hydrolases); EC 3.1.4.- (phosphodiesterase V); EC 4.6.1.2 (Guanylate Cyclase)

L46 ANSWER 59 OF 63 MEDLINE
ACCESSION NUMBER: 2001014014 MEDLINE
DOCUMENT NUMBER: 20494489 PubMed ID: 11183578

[redacted]

TITLE: Sildenafil in primary pulmonary hypertension.
AUTHOR: Prasad S; Wilkinson J; Gatzoulis M A
SOURCE: NEW ENGLAND JOURNAL OF MEDICINE, (2000 Nov 2) 343 (18) 1342.
Journal code: 0255562. ISSN: 0028-4793.
PUB. COUNTRY: United States
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001102
CONTROLLED TERM: Check Tags: Case Report; Human; Male
*3',5'-Cyclic-GMP Phosphodiesterase: AI, antagonists & inhibitors
Administration, Oral
Adult
***Hypertension, Pulmonary: DT, drug therapy**
*Phosphodiesterase Inhibitors: TU, therapeutic use
*Piperazines: TU, therapeutic use
CAS REGISTRY NO.: **139755-83-2 (sildenafil)**
CHEMICAL NAME: 0 (Phosphodiesterase Inhibitors); 0 (Piperazines); EC 3.1.4.35 (3',5'-Cyclic-GMP Phosphodiesterase)

L46 ANSWER 60 OF 63 MEDLINE
ACCESSION NUMBER: 2000298279 MEDLINE
DOCUMENT NUMBER: 20298279 PubMed ID: 10839936
TITLE: Sildenafil can increase the response to inhaled nitric oxide.
AUTHOR: Bigatello L M; Hess D; Dennehy K C; Medoff B D; Hurford W E
CORPORATE SOURCE: Departments of Anesthesia and Critical Care, Respiratory Care Services, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114, USA.. lbigatello@partners.org
SOURCE: ANESTHESIOLOGY, (2000 Jun) 92 (6) 1827-9.
Journal code: 1300217. ISSN: 0003-3022.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000720
Last Updated on STN: 20000720
Entered Medline: 20000711
CONTROLLED TERM: Check Tags: Case Report; Female; Human; Support, Non-U.S. Gov't
Administration, Inhalation
*Anoxemia: DT, drug therapy
Anoxemia: ET, etiology
Anoxemia: PP, physiopathology
Drug Synergism
Heart Septal Defects, Atrial: CO, complications
Hypertension, Pulmonary: CO, complications
Middle Age
Nitric Oxide: AD, administration & dosage
*Nitric Oxide: TU, therapeutic use
*Phosphodiesterase Inhibitors: TU, therapeutic use
*Phosphoric Diester Hydrolases: ME, metabolism
*Piperazines: TU, therapeutic use
Pulmonary Gas Exchange: DE, drug effects
CAS REGISTRY NO.: 10102-43-9 (Nitric Oxide); **139755-83-2 (sildenafil)**
CHEMICAL NAME: 0 (Phosphodiesterase Inhibitors); 0 (Piperazines); EC 3.1.4

(Phosphoric Diester Hydrolases); EC 3.1.4.-
(phosphodiesterase V)

L46 ANSWER 61 OF 63 MEDLINE
ACCESSION NUMBER: 2000393941 MEDLINE
DOCUMENT NUMBER: 20368925 PubMed ID: 10908271
TITLE: Sildenafil as a selective pulmonary vasodilator in childhood primary pulmonary hypertension.
AUTHOR: Abrams D; Schulze-Neick I; Magee A G
CORPORATE SOURCE: Department of Paediatric Cardiology, Royal Brompton & Harefield NHS Trust, Sydney Street, London SW3 6NP, UK.
SOURCE: HEART, (2000 Aug) 84 (2) E4.
Journal code: 9602087. ISSN: 1468-201X.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000824
Last Updated on STN: 20010521
Entered Medline: 20000814

ABSTRACT:
Primary pulmonary hypertension is a rare disease of childhood, which carries a poor prognosis. Patients often present with severe exercise limitation, and untreated life expectancy is less than 1 year. Pharmacological intervention is directed towards reduction of the raised pulmonary artery pressure with vasodilator treatment, initially with calcium antagonists, although more recently long term prostacyclin treatment has shown benefit in some patients. Heart-lung transplantation remains an option for children with severe disease refractory to therapeutic treatment. A 4 year old Bangladeshi girl with dyspnoea, cyanosis, and signs of a low cardiac output, is described. Initial treatment with prostacyclin was gradually reduced, and maintenance treatment with oral sildenafil (Viagra; Pfizer) instituted. At follow up 3 months later, her exercise capacity was greatly improved and she continues to enjoy a good quality of life without obvious side effects. In view of the encouraging initial results, this may become an acceptable adjunct in treating this patient group.

CONTROLLED TERM: Check Tags: Case Report; Female; Human
Antihypertensive Agents: TU, therapeutic use
Child, Preschool
Epoprostenol: TU, therapeutic use
***Hypertension, Pulmonary: DT, drug therapy**
*Phosphodiesterase Inhibitors: TU, therapeutic use
*Piperazines: TU, therapeutic use
Treatment Outcome
*Vasodilator Agents: TU, therapeutic use
CAS REGISTRY NO.: **139755-83-2 (sildenafil)**; 35121-78-9 (Epoprostenol)
CHEMICAL NAME: 0 (Antihypertensive Agents); 0 (Phosphodiesterase Inhibitors); 0 (Piperazines); 0 (Vasodilator Agents)

L46 ANSWER 62 OF 63 MEDLINE
ACCESSION NUMBER: 1999349821 MEDLINE
DOCUMENT NUMBER: 99349821 PubMed ID: 10422958
TITLE: Sildenafil ameliorates effects of inhaled nitric oxide withdrawal.
AUTHOR: Atz A M; Wessel D L
CORPORATE SOURCE: Department of Cardiology, Children's Hospital, Boston, Massachussetts 02115, USA.
CONTRACT NUMBER: FDR-001316-01 (FDA)
P30HD27805 (NICHD)
SOURCE: ANESTHESIOLOGY, (1999 Jul) 91 (1) 307-10.

Journal code: 1300217. ISSN: 0003-3022.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990816
Last Updated on STN: 19990816
Entered Medline: 19990805
CONTROLLED TERM: Check Tags: Case Report; Female; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*3',5'-Cyclic-GMP Phosphodiesterase: AI, antagonists & inhibitors
Administration, Inhalation
Cyclic GMP: ME, metabolism
Hypertension, Pulmonary: CI, chemically induced
Infant
Infant, Newborn
Nitric Oxide: AD, administration & dosage
*Nitric Oxide: AE, adverse effects
*Phosphodiesterase Inhibitors: PD, pharmacology
*Piperazines: PD, pharmacology
*Substance Withdrawal Syndrome: PC, prevention & control
CAS REGISTRY NO.: 10102-43-9 (Nitric Oxide); **139755-83-2 (sildenafil)** ; 7665-99-8 (Cyclic GMP)
CHEMICAL NAME: 0 (Phosphodiesterase Inhibitors); 0 (Piperazines); EC 3.1.4.35 (3',5'-Cyclic-GMP Phosphodiesterase)

L46 ANSWER 63 OF 63 MEDLINE
ACCESSION NUMBER: 1999176424 MEDLINE
DOCUMENT NUMBER: 99176424 PubMed ID: 10078538
TITLE: Effects of sildenafil citrate on human hemodynamics.
AUTHOR: Jackson G; Benjamin N; Jackson N; Allen M J
CORPORATE SOURCE: Guys and St. Thomas Hospital, London, United Kingdom.
SOURCE: AMERICAN JOURNAL OF CARDIOLOGY, (1999 Mar 4) 83 (5A) 13C-20C.
Journal code: 0207277. ISSN: 0002-9149.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990326
Last Updated on STN: 19990326
Entered Medline: 19990318

ABSTRACT:
Nitric oxide (NO) induces the formation of intracellular cyclic guanosine monophosphate (cGMP) by guanylate cyclase. Sildenafil, which selectively inhibits phosphodiesterase type 5 (PDE5) found predominantly in the corpora cavernosa of the penis, effectively blocks the degradation of cGMP and enhances erectile function in men with erectile dysfunction. The NO-cGMP pathway also plays an important role in mediating blood pressure. It is, therefore, possible that the therapeutic doses of sildenafil used to treat erectile dysfunction may have clinically significant effects on human hemodynamics. Three studies were undertaken to assess the effects of intravenously, intra-arterially, and orally administered doses of sildenafil on blood pressure, heart rate, cardiac output, and forearm blood flow and venous compliance in healthy men. A fourth study evaluated the hemodynamic effects of intravenous sildenafil in men with stable ischemic heart disease. In healthy men, significant ($p < 0.01$) decreases in supine systolic and diastolic blood pressures were observed with intravenous sildenafil (20, 40, and 80 mg) at the end of the infusion period when plasma

levels of sildenafil were highest (mean decreases from baseline of 7.0/6.9 and 9.2/6.7 mm Hg, for the 40- and 80-mg doses, respectively). These changes were transient and not dose related. Modest reductions in systemic vascular resistance also were observed (maximum decrease 16%), although heart rate was not affected by sildenafil administration when compared with placebo. Single oral doses of sildenafil (100, 150, and 200 mg) produced no significant changes in cardiac index from 1-12 hours postdose between placebo- and sildenafil-treated subjects. The approved dosage strengths of sildenafil citrate are 25 mg, 50 mg, and 100 mg. The 80-mg intravenous dose and the 200-mg oral dose of sildenafil produced comparable plasma levels at twice the maximum therapeutic dose (recommended range, 25-100 mg). After brachial artery infusion of sildenafil (up to 300 microg/min), there was a modest vasodilation of resistance arteries and a reversal of norepinephrine-induced preconstriction of forearm veins. These hemodynamic effects were similar to but smaller in magnitude than those of nitrates. In a small pilot study of men with ischemic heart disease, decreases from baseline in pulmonary arterial pressure (-27% at rest and -19% during exercise) and cardiac output (-7% at rest and -11% during exercise) were observed after 40-mg intravenous doses of sildenafil. Sildenafil was well tolerated by subjects and patients in all studies, with headache and other symptoms of vasodilation the most commonly reported adverse effects of treatment. Modest, transient hemodynamic changes were observed in healthy men after single intravenous or oral doses of sildenafil even at supratherapeutic doses. In men with stable ischemic heart disease, sildenafil produced modest effects on hemodynamic parameters at rest and during exercise.

CONTROLLED TERM: Check Tags: Human; Male
Administration, Oral
Aged
Arm: BS, blood supply
Blood Flow Velocity: DE, drug effects
Blood Pressure: DE, drug effects
Exercise Test
Heart Rate: DE, drug effects
*Hemodynamics: DE, drug effects
Injections, Intra-Arterial
Injections, Intravenous
Middle Age
*Myocardial Ischemia: PP, physiopathology
Phosphodiesterase Inhibitors: AD, administration & dosage
Phosphodiesterase Inhibitors: AE, adverse effects
*Phosphodiesterase Inhibitors: PD, pharmacology
Pilot Projects
Piperazines: AD, administration & dosage
Piperazines: AE, adverse effects
*Piperazines: PD, pharmacology
Reference Values
Single-Blind Method
Stroke Volume: DE, drug effects
Time Factors
Vascular Resistance: DE, drug effects

CAS REGISTRY NO.: **139755-83-2 (sildenafil)**

CHEMICAL NAME: 0 (Phosphodiesterase Inhibitors); 0 (Piperazines)

=> fil reg
FILE 'REGISTRY' ENTERED AT 15:11:03 ON 18 MAR 2003

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 17 MAR 2003 HIGHEST RN 499763-93-8
DICTIONARY FILE UPDATES: 17 MAR 2003 HIGHEST RN 499763-93-8

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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L48 1 139755-83-2
(139755-83-2/RN)

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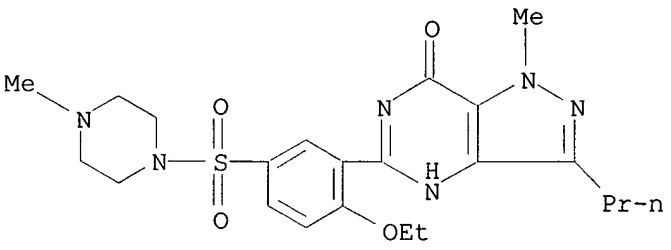
L48 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN **139755-83-2** REGISTRY
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrazolo[4,3-d]pyrimidine, piperazine deriv.
OTHER NAMES:
CN 5-[2-Ethoxy-5-(4-methyl-1-piperazinylsulfonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one
CN Sildenafil
FS 3D CONCORD
MF C22 H30 N6 O4 S
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: WHO



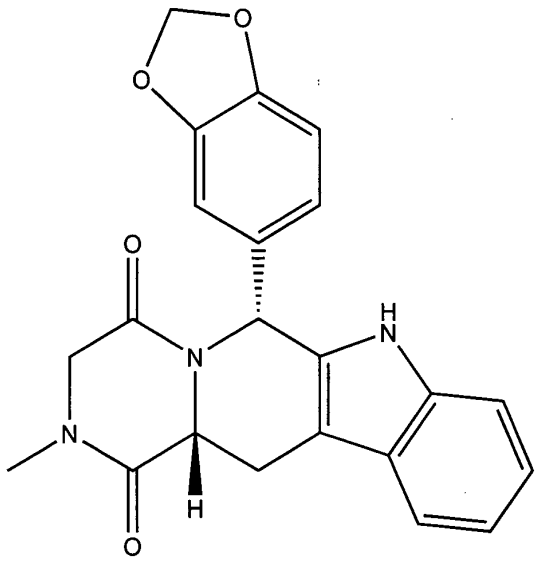
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

379 REFERENCES IN FILE CA (1962 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
382 REFERENCES IN FILE CAPLUS (1962 TO DATE)

FILE 'HOME' ENTERED AT 15:11:11 ON 18 MAR 2003

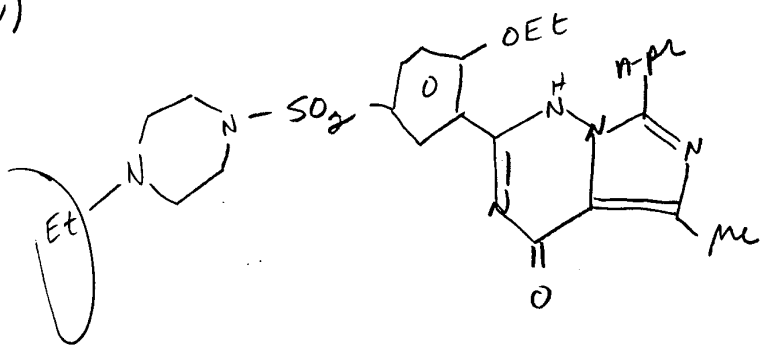
5,874,437

b)



(6r,12ar)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2'1':6,1]pyrido[3,4-b]indole-1,4-dione

c)



2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-
5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one